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ARCHIVES OF SURGERY

The Western Surgical Association—Its Past, Present, and Future
Everett P. Coleman

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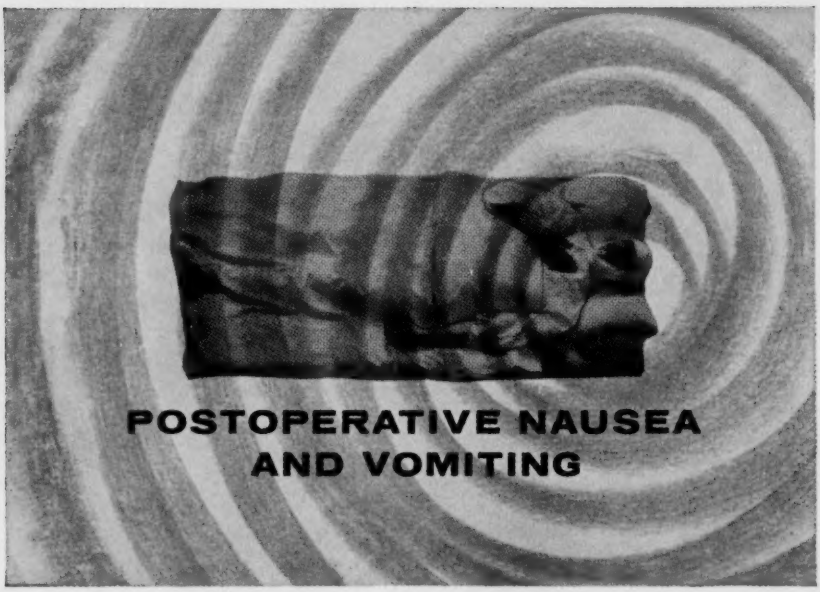

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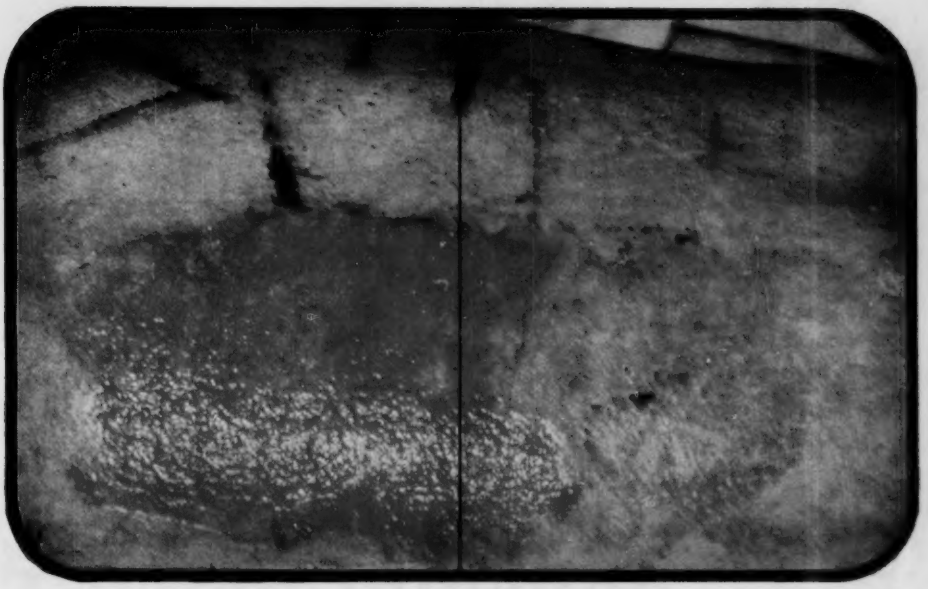

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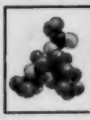

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The Western Surgical Association—Its Past, Present, and Future

EVERETT P. COLEMAN, M.D., Canton, Ill.

The honor you have conferred in electing me to this high office is one which I shall always treasure. In common with all of you, I belong to a number of other surgical organizations, all of them excellent ones and of high rating, but I appreciate my membership in the Western most of all. As Dr. Donald McRae said many years ago: "The presidency of the Western is a greater honor than being President of either the American Medical Association or the American College of Surgeons; it is a more difficult office to attain." I, too, regard it as such.

During my term as Recorder I have looked over most of the old *Transactions* and, among other things, have read the presidential addresses of many years gone by. I find that they follow a general pattern. The new presidents have usually been surprised when elected and have shown a sense of humility over the high honor which they have received. I echo both these sentiments. After discussing some of the surgical problems of the day, they have usually completed the address by making some comments on changes they felt should take place in medical education. In respect to this latter expression, and having the courage of ignorance, being in no way connected with medical education, I am going to make a few similar comments. Before doing this, however, I want to call attention to some of the things that the members of this Association have done, going back to the early days of the organization, to make a few comments about its function at the present time as I see it, and to venture one or two predictions as to its future.

Presidential address read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

The Western Surgical and Gynecological Association was organized in the year 1891 at Topeka, Kan., with Dr. S. S. Todd, of Kansas City, Mo., as president. With the exception of two years during wartime, in 1942 and 1943, it has met annually ever since. At the 1905 meeting in Kansas City, Dr. Arthur Hertzler was chairman of the Committee on Arrangements, and he dropped the term Gynecological from the title and left it as the Western Surgical Association. This seemed to meet with the approval of the membership, and the name has remained that ever since. Only once since then was the term "and Gynecological" used and that was in the title of the *Transactions* of 1918.

Going over some of the older *Transactions,* one is impressed with the number of changes that have taken place: first, of course, the tremendous advances in surgery during the past 50 years; second, the effect of the members of this society on surgical progress, and, third, the change in the type of pathology encountered in the practice of surgery over this period.

In my early days in the Association, I felt a sense of awe and admiration for the famous men who at that time constituted its leaders, and they were famous men. That was still in the days of the surgical giants—truly pioneer surgeons, such as Mayo, Harris, and Murphy, of this society, and I might include Deaver and Crile, who have been our guest speakers, and who, by their vitality, energy, and wisdom, entered into a field where true science had thrown only a glimmer of light. With real courage these men disseminated that light to such an extent that those of us who are simply followers have had a much easier path. With some of the dark spots more brightly illuminated, we have found a type of work that had once been very difficult made comparatively simple as a result of their efforts. Interestingly enough, the two men who have contributed the largest number of discussions have sons who are among our present members: Dr. B. B. Davis, of Omaha, and Dr. C. W. Mayo, of Rochester. In reading the discussions, one has the impression that they are often more instructive than the original papers.

In the old *Transactions* many problems and new ideas are recorded which, in the light of present knowledge, appear obvious but which in those days, with their limited diagnostic facilities, were indeed difficult problems to solve. Many things which we take for granted, and some of which we have discarded, were new discoveries to these men, and any study of their problems and conclusions reveals evidence of men of genius and ability, with a capacity to turn out a tremendous volume of work, and the idealism to evaluate their results and to report on them honestly. We are carrying on at the present time largely on the momentum they furnished. In the early days of this Association the members were mainly clinical surgeons, although some were also teachers in medical schools, largely on a part-time basis. While many of their conclusions were based on clinical judgment, one is impressed with the excellence of that judgment. Some of their ideas are acceptable at the present time and have contributed to our progress; others have been discarded, but both extremes are interesting, and I shall enumerate a few of them. Among the problems they discussed were syphilis of the stomach and Charcot's joint. Later on Whitman's method of treating fracture of the neck of the femur occupied much space, and, still earlier, much discussion was brought out with reference to the necessity of using a new discovery called x-rays in the treatment of fractures. The frequent complication of wound infection was the sword of Damocles over the head of every surgeon of only a generation ago. Tuberculosis of the bones and joints and a wonderful new anesthetic, which was a combination of ethyl chloride, chloroform, and ether, were among the subjects discussed.

In 1935 Dr. Carl Black was chairman of a committee which attempted to standardize the names of the various surgical operations. This committee tried to use names that suggested the proper anatomy and pathology involved and to get away from names of the surgeons who first described the operation. A number of booklets were printed and given to the membership and sent to all medical college libraries, but the temptation to have one's own name attached to an operation or procedure was too great, and the committee's work has been forgotten.

Dr. Black also published a small book with the names and pictures of all the membership up to that date, 1930, with a list of their contributions in papers and discussions given before this Association. This could be repeated to advantage.

A generation ago one of the major surgical problems was that of appendicitis. It was apparently more prevalent than it is now, and much discussion was held as to the relative merits of the Ochsner and the Murphy method of treating appendiceal peritonitis. In other words, should the patient with appendicitis be operated upon as soon as the diagnosis was made, whether it was three, four, five, or six days after the onset, or should the late case be treated conservatively? Incidentally, it has been my

unfortunate privilege to have gone through both these extremes. Our members were also troubled by a condition that most of us no longer recognize, that is, chronic appendicitis. They referred to it frequently in their papers and discussions and regarded it as a well-defined clinical entity. Dr. Jabez Jackson, one of our very forceful and prominent members, described a congenital band involving the cecum, which was termed "Jackson's membrane," and this for a long time was thought to account for many chronic symptoms which were probably due to gallbladder or stomach disease. Many series of cases were reported, with remarkable results following the separation of this membrane. Apparently, the power of mental suggestion was just as great then as it is now. There have been many discussions as to the relative merits of cholecystectomy and cholecystostomy, and that was a common title in surgical papers of a few years ago. Dr. Alexander Hugh Ferguson, a very prominent surgeon of Chicago and president of this Association in 1903, wrote an interesting article decrying the use of cathartics in the treatment of appendicitis. The one commonly used at that time, magnesium sulfate U. S. P. (Epsom salt), he thought was definitely detrimental to the patient who had appendicitis, and he felt that its use was so dangerous that it should not be allowed to be given in this condition. Instead, he recommended a healing dose of castor oil.

A few years later there was a decided change in the content of the papers read. About 1916 a very interesting paper was given on animal experimentation work which indicated the feasibility of intratracheal anesthesia in thoracic surgery in dogs, especially with reference to the formation and correction of diaphragmatic hernia in dogs. This idea seemed not to fall on fertile soil, probably because of the type of anesthesia available in those days. It was not until much more recently that this early thought developed into the practical ideas used at the present time. But, again, we can see over the years gradual changes brought about largely by members of this Association, the fundamental principles of which have remained unaltered and which have been the foundation stone of progress in some particular fields. For example, Dr. Lockwood, of Pasadena, in 1918 read an excellent paper on the connection between the development of cancer and the use of tobacco—not cancer of the lung so much as cancer of the mouth, lip, and stomach. The present concept of the treatment of infections and injuries of the hand was first given before this society in discussion by Dr. Allen Kanavel, and the recent papers of his associates, Drs. Koch and Mason, not only have revolutionized the treatment of open and contaminated wounds but have developed the principles of treatment of these conditions which have become standardized methods at the present day. In 1923 Gregory Connell wrote the first article which I have been able to find questioning the diagnosis of chronic appendicitis and throwing doubt on the possibility of there being such a clinical entity. In the same year Dr. Thomas Orr Sr. gave his paper on intestinal obstruction, which, to my knowledge, is the first scientific contribution to the cause of the mortality of this disease, a recognition of the changes in blood chemistry that take place, and made suggestions which have led to the present method of it management. The first article published in this country demonstrating that perforated peptic ulcer is usually accompanied by air in the free peritoneal cavity was read before this Association in 1924 by Drs. Vaughn and Brams, and the papers of Speed and of Cubbins and Vernon David, who were pioneers in the modren treatment of fractures, show the early trend toward accuracy and completeness of reduction in fracture management. Our early clinical surgeons differed greatly from the present generation, when one almost needs a degree in veterinary medicine to comprehend the animal work which is being done in the large teaching centers.

I have already stated that, in going over these reports, one is impressed by the fact that many of the advances in the science of

surgery which have led to our present-day concept of its use were developed by men who were members of this organization. I believe that applies largely at the present time also, for some of the pioneers in cardiac surgery, thoracic surgery, and vascular surgery are members of this Association, and we as a group are still carrying the torch of progress in a constant effort to increase our knowledge and that of our fellow surgeons.

I also commented that most presidential addresses have included some statement as to changes that are needed in the teaching of the medical student, the intern, and the resident. None of us have come anywhere near attaining the perfection we have tried to reach, and, although we may be unable to see faults in ourselves, we can very readily detect them in others. As we grow old enough to become critical of the younger generation, we can see in it the faults that we could not see in ourselves at that period of life. It is probably presumptuous, and perhaps foolhardy, for one who is not connected with teaching to address a group composed largely of teachers, and in any way to attempt to find fault with the product they are bringing forth. But the problems of surgery are changing in many ways, and it is no longer enough to standardize hospitals and eliminate fee splitting and other evils which must constantly be combatted, for new problems have appeared which apply to the younger generation more than to their elders.

As an answer to the threat of Government control, or complete socialization of medicine, prepayment hospitalization insurance appeared. It was planned as a method of budgeting against hospital expenses, particularly for the low-income group. The widespread acceptance of this idea has brought about problems which were unforeseen when the plan was first started. The rapid growth of Blue Cross, Blue Shield, and other voluntary insurance plans has been followed by some, less desirable but popular, union centers, and now by the Government's new "Medicare" program. All these have their advantages and their drawbacks. They do result in over 120,000,000 people being covered by some type of sickness insurance. Many of these persons can now afford to have necessary medical and surgical care which they might formerly have postponed or neglected for economic reasons. Many of them desire hospital care for conditions which could equally well be treated in the home or office, and a great demand is now being developed for a complete type of examination, with expensive and numerous laboratory tests and a multiplicity of x-ray pictures. The insurance case is now able to have the doctor of his own choice care for him rather than being a clinic case on a charity service. This has some obvious advantages, but it is decidedly interfering in some places with the resident training program by leaving an insufficient number of ward or teaching cases.

Although many of the public are insured, there is a large number of the middle- and lower-income group who are not insured, and these complicate the financial problem of hospitalization. The young intern or resident is taught the desirability of many laboratory procedures. He is so familiar with them that he becomes dependent upon them, when equal diagnostic accuracy could be had from a careful history and physical examination.

When he enters practice as a general practitioner, with one year internship, or as a Board-certified surgeon, he is all too likely to hospitalize all patients, to ignore the possibilities of the physical examination, and to order all known laboratory tests plus a very comprehensive series of x-rays. These are sometimes indicated and do have definite advantages. They should be used when properly indicated, but to be ordered routinely and indiscriminatly has several disadvantages. The main drawback is that of expense. If the patient is without insurance, the addition of $200 to $300 to his bill plus five to seven days of additional hospitalization may constitute a major financial catastrophe. If he is insured and this process becomes routine, as occurs

in many places, the insurance carrier has to revise its rates upward, as has happened to Blue Cross a few times. Any excessive increase in hospital insurance rates to cover unnecessary tests and x-rays defeats the purpose of hospital insurance, for it can easily be priced out of the market for the low-income patient. Recently one of our members found that a resident had ordered 20,000,000 units of penicillin daily for one patient for a period of 10 days, the indication being a mild postoperative fever of undetermined origin.

A part of any teaching program should include an attempt to instill in the trainee a sense of responsibility for the costs to be inflicted upon the patient or his insurance company. Unless this is accomplished, and soon, the prepayment insurance program may be seriously crippled, owing solely to lack of foresight on the part of the medical profession.

Another problem faced by the recent graduate who is attempting to qualify himself to do surgery is that of becoming Board-certified. In order to obtain certification, he has to have his three- to five-year residency in an approved hospital with some teaching facilities attached, and he is given opportunities to do a considerable amount of surgery and to observe the technique of those who have had more experience than he. However, with the tendency toward specialization, many a young man trained in general surgery is trained in just that, which means largely the surgery of the upper abdomen and thorax. There was a time, not too long ago, when a young man who was going to limit his work to surgery would have to locate in a city of some considerable size, if for no other reason than the fact that there, and only there, were hospital facilities plus adequate consultation available. With the present trend of the public to leave cities and move to suburban areas, and with new and modern hospitals being built in many small communities, there is an excellent opportunity for the well-trained young surgeon to locate in a smaller community, where with modern facilities he can do equally as good work as though he had remained in some teaching center and where his opportunities for developing a practice are much greater. Therefore, when he starts in a smaller community, he is probably the best-trained man in general surgery in that area. However, he cannot always limit his work to the type of surgery found in his residency. He may have to include the treatment of fractures and gynecology. I have seen several instances in which graduates from excellent teaching institutions were totally unprepared to take care of these important problems.

In some parts of the country gynecology is regarded as being surgery, and so is the management of fractures. There may be no qualified gynecologist within many miles, and there are not enough orthopedists in the country to take care of all the fractures that have to be managed. I feel that the well-qualified young general surgeon who has not had some experience in gynecology and in fractures is being put out under an unfair handicap, and that he should have a more rounded training in these two important subjects. It is quite true that he does not get these things in many institutions; I know of a few where he does not, and I feel that this is hardly a fair deal to him.

One last criticism, if I may call it that: When our young man who has just completed a residency in general surgery wants to be certified by the American Board of Surgery, he has to take two examinations. We have heard at our various meetings the report of our representative on the American Board of Surgery, telling how these young men, many of whom are not young men any longer but in their 30's, who have had a three- to five-year residency, and who have had some military service following an internship, attempt to take the Board examination and how a very high percentage fail to make the grade, with 22% failing the first examination and 28% the second, in 1955. This is a total of 50%, and there was a failure rate of 55.9% in 1956. It makes one wonder whether these

men, who have apparently had every opportunity to be well trained, might not be the victims of insufficient or inadequate training; and when we consider the dedicated services rendered by those who do conduct the examinations at a great cost of time and energy, it seems unjust to criticize them in any way. Some other cause must surely be responsible for such a high percentage of failures. Whatever the reason may be, surely some solution can be found to increase the percentage of successful candidates without in any way lowering the standards. If the candidates are really not qualified to pass this type of an examination, and if they are not of the caliber to become Board-certified surgeons, it should not take three years to find this out. I do not mean to imply that the standards should be lowered, but if, as some believe, we are now turning out a considerable surplus of surgeons, the elimination should start at the beginning of the training program rather than three years later. Having no connection with teaching, this thought is meant as a question, and not as an answer.

This organization has, during most of its existence, been a society of clinical surgeons, and largely of the outstanding ones in this part of the United States. We need in it a very definite percentage of teachers, and this addition has been made during the past several years. It is my considered opinion that we should, in our applicants for membership, return to the idea that the clinical surgeon should be given equal consideration with the men in university centers who are prolific writers and excellent teachers, but who cannot be used to replace entirely the clinical surgeon who cares for the surgical problems of the citizens of this country.

I am certain that the problems of the future will be solved as effectively as have those of the past, and that this Association will continue its function as the leading clinical surgical organization in the United States.

24 N. Main St.

Thyroid Cancer Biology

JOSEPH A. BUCKWALTER, M.D.; EDWARD E. MASON, M.D.; ROBERT D. ROWLEY, M.D., and ROBERT A. BROER, M.D., Iowa City

Introduction

Most articles concerned with the treatment of thyroid cancer have been based upon small numbers of patients. Discussions of treatment have been dogmatic, with little reference to the biology of the disease. This paper is a study of the biology of this neoplasm reflected in clinical findings and its course. A search has been made for pathognomonic signs or symptoms. As surgical consultants to a thyroid clinic, we must frequently make decisions regarding the indications for surgery in patients with diffuse or multinodular goiter. The need for more reliable criteria upon which to base such decisions was one of the motivations in this investigation. The well-established indication of a solitary nodule applies only in a minority of patients seen.

Materials and Methods

One hundred seventy-six patients seen at the University Hospitals from 1928 to 1957 with carcinoma of the thyroid gland provided the clinical material for this study. In 132 cases the diagnosis was established at the University Hospitals, while in 42 it was established prior to admission. Relevant data were obtained from case, operating-room, thyroid-clinic, radiation-laboratory and private-outpatient records. Additional information came from the patients, their physicians, and other hospitals. The data were transferred to punch cards. Machine methods of sorting facilitated analysis of the findings. Multiple histologic sections of primary and secondary lesions were reviewed by us without knowledge of the previously established diagnosis. The lesions were classified as follicular, papillary, or poorly differentiated. The general principles of classification suggested by Warren and Meissner [4] were followed.

From the Department of Surgery, State University of Iowa College of Medicine.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 21, 1957.

The predominant pattern of the 62 follicular adenocarcinomas was similar to that of normal thyroid. Single well-differentiated cuboidal and columnar epithelial cells were arranged in acini, many of which contained colloid. Mitoses were infrequent, and pleomorphism was minimal. Blood vessel, lymphatic, and capsular invasion and spread to regional lymph nodes and distant sites were noted. The presence of one or more of these findings was required for a diagnosis of malignancy. The minor anatomical and biological differences among lesions within this group seem an insufficient basis for subclassification. Attempts to do so only cause confusion, obscuring important prognostic and therapeutic considerations.

In the 63 papillary lesions the predominant pattern was one of individual resting thyroid epithelial cells, arranged in single layers about thin connective tissue stalks, which projected into different-sized and variously shaped acini. Colloid was minimal. Mitoses were rare, and cellular and nuclear pleomorphism was uncommon. Again, vascular, lymphatic, and capsular invasion and spread to regional nodes and distant sites were the criteria for malignancy.

The remaining 51 patients had poorly differentiated lesions. Two of these patients had Hurthle-cell and eight small-cell carcinomas. In 41 neoplasms cellular disorganization, cellular and nuclear pleomorphism, and mitotic activity were the predominant features. Abortive acini were occasionally noted. In several lesions, these were the only finding which made it possible to establish the epithelial, rather than the mesenchymal, origin. Little or no colloid was formed by these neoplasms.

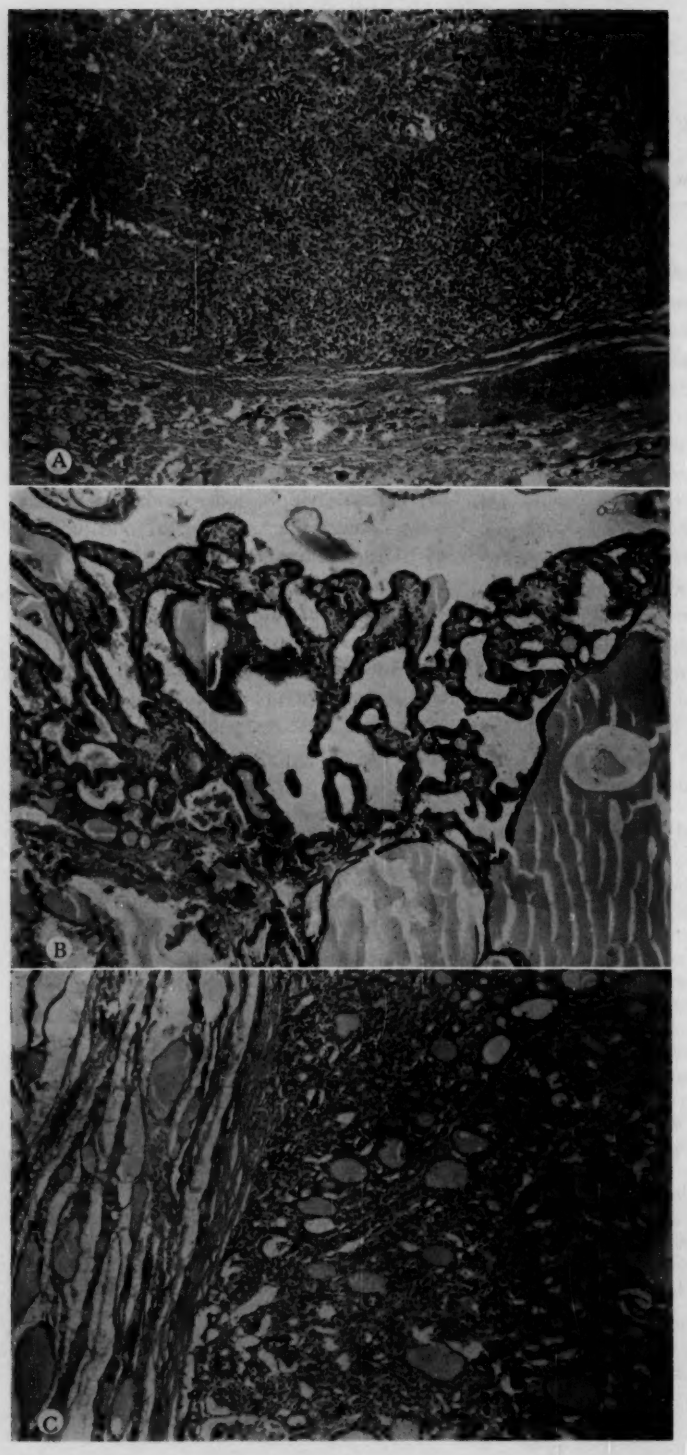

Fig. 1.—Follicular carcinoma in a 26-year-old woman; primary in left lobe; left cervical node involvement.

A, follicular pattern, primary; *B*, papillary pattern, primary; *C*, poorly differentiated pattern, primary.

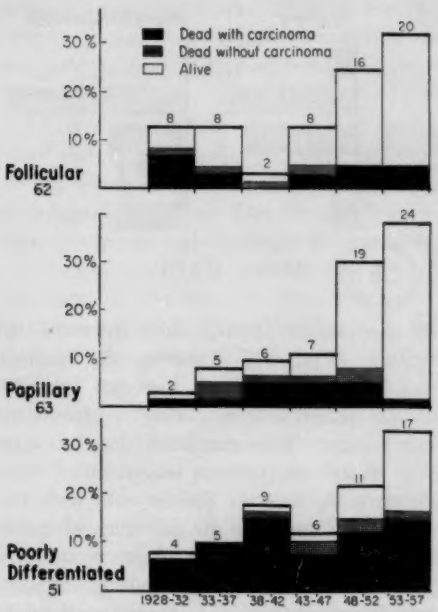

Fig. 2.—Number and percentage of patients with follicular, papillary, and poorly differentiated carcinoma, surviving and dead with and without carcinoma, by year of diagnosis.

Rarely does any thyroid carcinoma have a completely uniform histologic pattern. Morphological classification must be based upon the predominant histologic pattern. If a sufficient number of sections from any lesion are examined, one will usually find areas typical of follicular, papillary, and poorly differentiated adenocarcinoma. Wide variation may occur within the primary lesions, between the primary neoplasm and its metastases, or among separate metastases (Fig. 1).

Results

The progressive increase in the number of patients seen in each five-year period is to be noted (Fig. 2). The rapid increase during the past decade can be largely attributed to the introduction of new facilities (serum protein-bound iodine determinations and radioactive iodine) and the activation of a thyroid clinic composed of representatives of the Departments of Internal Medicine, Surgery, Radiology, and the Radiation Research Laboratory, in 1948. During this same 10-year period there has been a 20% decrease in surgical procedures performed for thyroid disease, and use of radioactive iodine has become the common therapy for toxicity. Surgery is being more and more limited to the diagnosis and treatment of thyroid malignancy. In Figure 2, patients known to have died with carcinoma are shown in solid black, and those dying of an unknown cause, by the shaded areas. The unshaded areas represent those patients who were living at the time of this investigation.

The number of patients in each age decade with each type of carcinoma and the median age for each type are indicated in Figure 3. The breakdown of these data by sex is shown by the superimposed solid and dotted lines for each lesion group. Patients with poorly differentiated carcinoma were the oldest, with the median age in the sixth decade of life, and those with follicular carcinoma were the youngest, with the median age in the fourth decade. When the 176 patients are considered as one group, the median age of female patients was a decade less than that of the male patients. The ratio of female to male patients was 3.0, being 1.0 for follicular lesions, and 1.2:1.0 for papillary and poorly differentiated lesions.

More than 85% of patients with follicular and papillary carcinomas complained of a mass in the neck, as compared with 75%

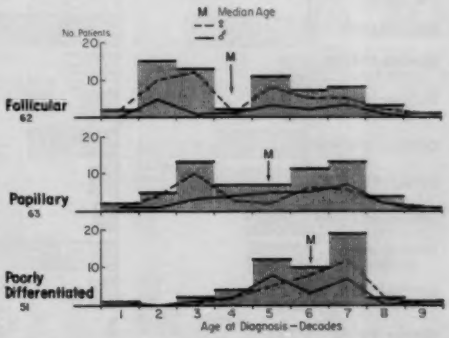

Fig. 3.—Age and sex incidence of patients with follicular, papillary, and poorly differentiated carcinoma.

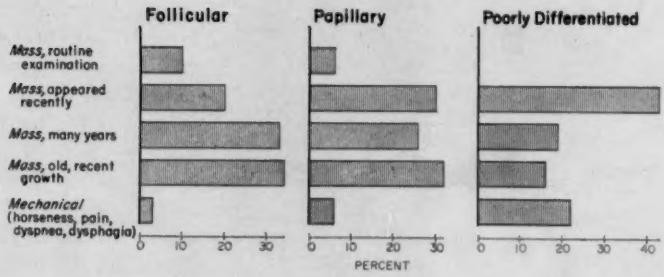

Fig. 4. — Chief complaints of patients with follicular, papillary, and poorly differentiated carcinoma.

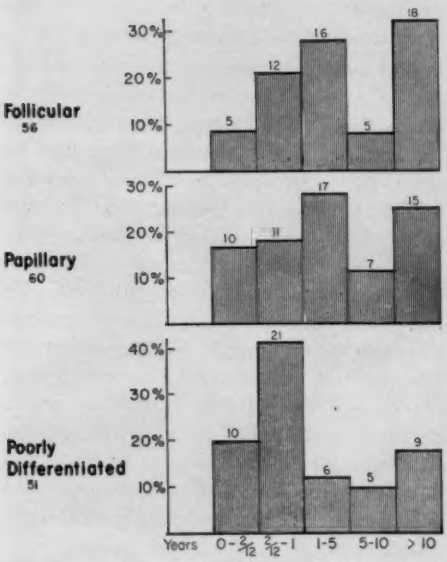

Fig. 5.—Duration of chief complaints prior to diagnosis.

of the patients with poorly differentiated lesions (Fig. 4). Hoarseness, dyspnea, dysphagia, or pain was reported by 22% of the patients with poorly differentiated carcinomas. The complaint that "a mass was found on routine examination" was reported in 10% of the patients with follicular and in 6% of the patients with papillary carcinoma; no such observations were made in the patients with poorly differentiated carcinomas. The commonest chief complaint of almost 50% of the patients with poorly differentiated carcinomas was a recent mass. A mass present many years and without any recent change was the chief complaint of 33% of the patients with follicular carcinoma, of 25% of the patients with papillary carcinoma, and of 20% of the patients with poorly differentiated carcinoma. Recent growth of a long-standing mass was reported by 34% of the patients

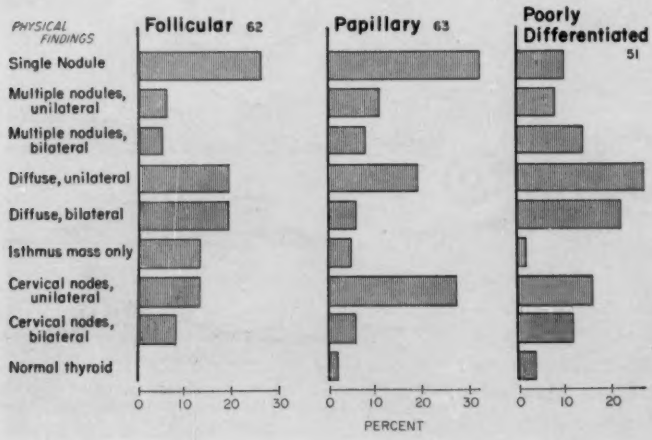

Fig. 6.—Physical findings in the neck at the time of admission to the University of Iowa Hospitals.

with follicular carcinoma, 32% of the patients with papillary carcinoma, and 16% of the patients with poorly differentiated carcinoma.

Although much less common than in the other two types, poorly differentiated carcinoma (Fig. 5) was found in patients with neck masses of more than 10 years' duration. Sixty per cent of poorly differentiated carcinomas occurred in patients with a chief complaint of less than one year's duration, as compared with approximately 30% for each of the differentiated types of carcinoma.

A single nodule was observed at admission three or four times as often in patients with follicular and papillary carcinoma as in patients with poorly differentiated carcinoma (Fig. 6). Sixty-five, or 37%, of the patients had either unilateral or bilateral diffuse enlargement of the thyroid. Thirty of the patients (17%) had multiple nodules. Cervical lymphadenopathy was twice as common in the patients with papillary carcinoma as in the patients with the other two types. Thirteen patients with poorly differentiated carcinomas had unilateral and three bilateral vocal cord paralysis. Seven of the patients with follicular and five with papillary carcinoma had unilateral cord paralysis at admission. Pulmonary metastases were present in four children who had follicular carcinoma at admission. Four adult patients with follicular carcinoma had bone metastases. Demonstrable bone metastases have not been seen in children. Pulmonary metastases were noted in two patients and bone metastases in one patient with papillary carcinoma. Of patients with poorly differentiated lesions, two had pulmonary, two bone, and six soft-tissue extension at the time of admission.

There was a history of previous goiter in six patients with papillary lesions, two with poorly differentiated carcinoma, and in none with follicular lesions. Nine patients, three with each lesion, had had external irradiation to the neck. Five of the patients with follicular, four with papillary, and none with poorly differentiated carcinoma were or recently had been pregnant. Two patients with follicular lesions gave a family history of thyroid carcinoma. A family history of goiter was obtained in three of the patients with follicular and in three with papillary neoplasms.

Figure 7 shows that 43% of patients with follicular carcinoma, 40% with papillary carcinoma, and 17% with poorly differentiated carcinoma were incorrectly regarded as having benign lesions, whereas a correct diagnosis of malignancy was made in 75% of patients with poorly differentiated, 37% with follicular, and 46% with papillary car-

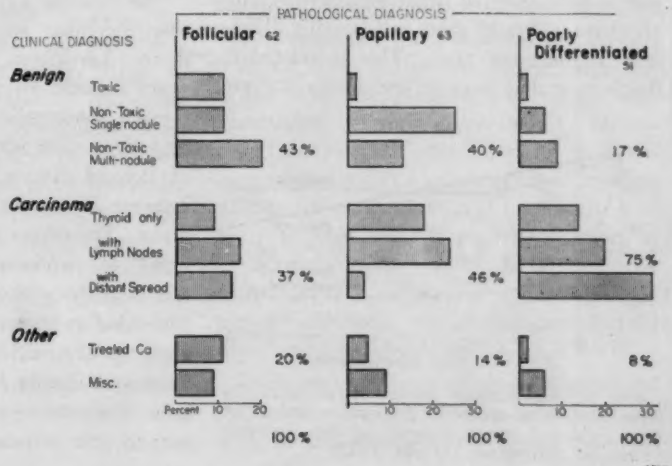

Fig. 7.—Clinical diagnoses at the time of admission to the University of Iowa Hospitals. *Other* includes patients diagnosed prior to their University Hospital admission.

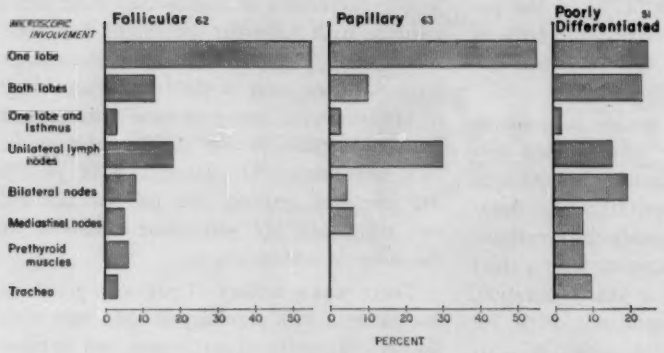

Fig. 8.—Spread of lesions indicated by histopathologic examination of surgical specimens.

cinoma. In the "other" group the diagnosis was established most frequently in patients with follicular lesions (20%).

Figure 8 shows that papillary carcinomas tended to spread to lymph nodes and infrequently presented a local problem related to invasion of the trachea, prethyroid muscles, and adjacent structures, as constrasted with poorly differentiated lesions. Both lobes of the thyroid gland were involved in 8, or 13%, of the patients with follicular carcinoma, in 6, or 10%, of the patients with papillary carcinoma, and in 12, or 24%, of the patients with poorly differentiated carcinoma.

The survivorship curves (Fig. 9) indicate the most significant figures for the first few years due to the small number of cases. The curves for follicular and for poorly differentiated carcinoma have a similar shape, although there is a striking difference in mortality rates. This is related to the finding that most of the deaths that are

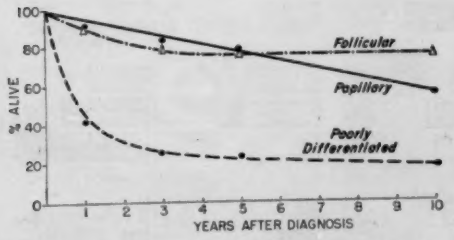

Fig. 9.—Survivorship curves. Reproduced, by permission, from article by J. Berkson and R. P. Gage published in the *Journal of the American Statistical Association* (47:501, 1952).

going to occur do so within the first three to five years for both types of lesions. In contrast, the patients with papillary carcinoma had a death rate which appears to be almost linear over the period studied. The meaning of this observation must await study of a larger number of patients observed for more than 10 years.

Comment

Differences in the biology of the lesions establish the importance of distinguishing between well-differentiated (follicular and papillary) and poorly differentiated carcinomas. Although the distinction between follicular and papillary carcinomas is less clear, the findings suggest that it is possible and desirable to recognize these two types of well-differentiated carcinoma.

The possible explanations for the markedly increased numbers of patients with thyroid carcinoma seen during the past 10 years include an increasing awareness of thyroid abnormalities, increasing use of radioactive iodine for diagnosis and treatment of thyroid disease, and perhaps an actual increase in the incidence of thyroid carcinoma. The relative frequencies of the three types of carcinoma have not materially changed, even though the total incidence has. One exception to this statement is the apparent higher incidence of follicular lesions seen during 1928 to 1939. In some of these cases no tissue was available for our perusal. It is possible that this apparent

higher incidence may, in part, be attributed to differing diagnostic criteria.

The incidence of iodine deficiency disease of the thyroid has decreased, and the therapeutic use of radioactive iodine has increased during these 30 years. These are two factors that theoretically might influence the type of carcinoma seen. No convincing evidence of any such influence has appeared.

The age and sex distribution and behavior of poorly differentiated carcinoma of the thyroid are similar to these factors in cancer of some other organs. By contrast, both follicular and papillary carcinomas are commoner in young female patients. This coincides with the greater activity of the thyroid early in life and the higher incidence of hyperthyroidism in women, and suggests the possibility of a relationship between recurring hyperplasia of the thyroid and carcinomatous change.

The need for criteria useful in establishing operative indication in nontoxic goiter has not been entirely satisfied. A mass in the neck was the chief entrance complaint in 75% of the patients. This complaint was much commoner in patients with follicular and papillary carcinoma than in those with poorly differentiated lesions. Approximately 20% of the patients with poorly differentiated carcinoma stated that a mass had been present for more than 10 years. This may indicate recent malignant change in a long-standing multinodular goiter or slow progression of the neoplasm. A mass was more frequently present longer than 10 years in patients with follicular carcinoma than in patients with papillary lesions. This, together with the finding that the diagnosis of follicular carcinoma was more frequently established before their University Hospitals admission than was the diagnosis of papillary carcinoma suggests the possibility that follicular lesions progress slowly and are diagnosed later than papillary lesions.

A solitary nodule is found most frequently in patients with papillary carcinoma, less frequently in patients with follicular lesions, and rarely in patients with poorly differentiated carcinomas. There is also an apparent proclivity for papillary carcinoma to involve unilateral cervical lymph nodes. This occurred twice as often in papillary as in follicular or poorly differentiated lesions. In contrast, there appeared to be no differences in the frequency of bilateral cervical adenopathy. The finding of bilateral diffuse enlargement of the thyroid four times as often with follicular and poorly differentiated lesions as with papillary lesions has several possible explanations. This fits well with findings compatible with thyrotoxicosis in approximately 10% of the patients with follicular carcinoma (Fig. 7). It suggests that follicular carcinoma may be related to normal or hyperplastic thyroid physiologically as well as anatomically. The curious behavior of these lesions in children with early pulmonary metastases, which appear to be peculiarly responsive to radioactive iodine treatment, fits well with this hypothesis.[2] The diffuse thyroid enlargement so frequently seen with poorly differentiated lesions is probably on a different basis. A recent mass, early mechanical symptoms (four times as frequent in poorly differentiated as in follicular and papillary carcinoma), frequent involvement of both thyroid lobes, relatively late lymph node involvement, early invasion of adjacent soft tissues, all are consistent with the rapid, locally invasive growth and more lethal course of undifferentiated carcinoma.

The examiner concluded that the thyroid was not abnormal in one patient with follicular and two patients with poorly differentiated lesions. These findings merely point out that the absence of thyroid enlargement does not exclude malignancy. One of these, a patient admitted because of inability to void secondary to destruction of the second lumbar vertebra by a metastasis from a poorly differentiated carcinoma of the thyroid, with no conspicuous thyroid mass, has previously been reported.[3]

With the exception of x-ray findings of metastatic disease, laboratory procedures were of little value in establishing the diag-

nosis. Scintigrams suggest that a nodule may be carcinomatous when less iodine is accumulated there than in the remainder of the gland. Adenomas and cysts that do not take up iodine and the occasional follicular carcinoma which does take up iodine make this examination less than diagnostic.

The clinical impression was only slightly better than a guess except for the undifferentiated lesions, which, because of local or distant growth, were often obvious carcinomas. If the guess was wrong, the clinicians responsible were aware that it was only a guess, as is evidenced by the fact that the patients were operated upon often "to rule out carcinoma." It is interesting that 10% of the patients with follicular carcinoma were considered to be clinically mildly toxic, although the laboratory data were inconclusive. The diagnosis of toxicity has rarely been made when basal metabolic, protein-bound iodine, and radioactive iodine studies have been done.

Microscopic spread to unilateral lymph nodes occurred oftenest in papillary carcinomas, whereas bilateral spread occurred most frequently with poorly differentiated lesions. The fact that papillary carcinoma grows and kills slowly may obscure the importance of lymph node spread as a factor in the ultimate outcome in this disease.

Seventy-five per cent of the patients with undifferentiated carcinoma will die during the first three years following the diagnosis. If a patient survives these first three years, it appears that he has a good chance of being cured. A similar-shaped curve for follicular carcinoma shows that only 20% of the patients die during this first three-year period. Patients with papillary carcinoma continued to die during the 10-year period of the survival study, this type having approximately the same mortality rate as follicular carcinoma during the first three years. However, because of the relatively few patients subjected to the risk of dying for the total 10-year period, these data must be regarded as only suggestive. The other findings obtained in this study seem to be consistent with these survivorship curves. Thus, the relatively rapid-growing undifferentiated carcinoma, which appears to extend early to involve adjacent soft tissues, would be expected to cause rapid death. Because of the slow growth and extensive involvement of lymph nodes, the papillary lesions might be expected to have a survivorship curve such as that which has been found. The best prognosis might be anticipated in patients with follicular carcinoma, since this lesion appears to be very slow-growing and is characterized by less extensive lymph node involvement. A favorable result from radioactive iodine therapy occurring more frequently in follicular than in papillary and poorly differentiated lesions is consistent with the closer anatomical and physiological relationship of follicular lesions to normal thyroid.

Summary

The biology of thyroid carcinoma, as reflected by the clinical characteristics and the course of the disease in 176 patients, has been studied. On the basis of the predominant histologic pattern, the lesions were classified as follicular, papillary, and undifferentiated carcinomas. The findings indicate marked differences in the biologic behavior of well-differentiated and poorly differentiated carcinoma. Less striking, but none the less definite, differences were noted between follicular and papillary varieties of well-differentiated carcinoma. Any goiter, solitary or multinodular, unilateral or bilateral diffuse, must be viewed as possibly carcinomatous, especially if there are no signs of toxicity.

Survivorship curves show that about 10% of patients with follicular and papillary lesions die within the first year after diagnosis, as compared with 60% of patients with poorly differentiated carcinoma. The pooling of such data from similar institutions would make it possible to reach statistically significant conclusions concerning survivorship not possible with individual series.

University Hospitals.

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DISCUSSION

Dr. John E. Kearns, Evanston, Ill.: When I was asked to discuss this paper, I was extremely complimented, and after reading Dr. Buckwalter's essay I was further complimented. I felt particularly complimented because most of the data that he presented confirmed an essay that Dr. Davis and I presented three years ago at this meeting. It was the last paper presented on the last day, and I believe the following lantern slide will show you how I felt that day.

[Slide] "I listened to yours; why don't you listen to mine?" [Laughter] I hope you will all listen to Dr. Puestow's paper, which is the last one on the program this year.

[Slide] This is similar to Dr. Allen Graham's classification of about 1924. It answers the problem of papillary, follicular, alveolar, Hurthle-cell, and so on. We have found that papillary tumors metastasize as alveolar tumors, and Hurthle-cell tumors metastasize as both or either. At this time we presented the following classification. [Slide]

We felt very definitely that blood vessel, lymphatic, or invasive spread was of greater import than the histology of these tumors. We felt particularly that the hemangioinvasive type was the most malignant of these clinically rather benign tumors, and, of course, we put the undifferentiated cancers in a group by themselves, as did Dr. Buckwalter.

Further study has confused us in this area, and I should like to mention our group of 78 patients. We have had six deaths. It is interesting to note how these people die; I think we learn more from studying their deaths than we shall from the statistical data.

One death was due to a ruptured carotid artery on the seventh postoperative day. All these patients still had cancer at necropsy, and in all of our cases of death autopsy was done. X-ray therapy killed another, by causing a slough with mediastinitis in a patient who had a tracheostomy. Another patient was epileptic; he had a seizure and knocked over a lamp and burned to death. The fourth patient bled to death from a gastric hemorrhage and was signed out in the state of Illinois as "death due to generalized carcinomatosis from an adenocarcinoma of the thyroid." The state would not change the diagnosis. A fifth was operated upon elsewhere when I was ill. This man was a 30-year survivor. The first neck dissection took 12 hours, and the second took 8 hours. The man died on the second postoperative day, and the findings at autopsy were myocardial damage. The sixth of our patients died of anoxia from lungs filled with cancer, and this is the only patient who died of cancer. All the others died with cancer, but cancer was not the cause of death.

Dr. Horace J. McCorkle, San Francisco: It was a real privilege to be able to read Dr. Buckwalter's essay and to hear his presentation of the material.

Dr. Stuart Lindsay, professor of pathology at the University of California, recently made a survey of the patients operated upon in university hospitals between 1920 and 1954. There were 293 cases of cancer of the thyroid, and over half of these were predominantly of the papillary pattern. Many of the patients (over 60) have died of the cancer of the thyroid; so it is true, as the authors have said, that patients do die of cancer of the thyroid, and this is particularly true of those with undifferentiated types of lesions.

It is impossible for us to be certain in many cases, at the time of operation, which type of cancer we may be dealing with. The pathologist is helpful, but not infallible, with frozen-section microscopic studies. Sometimes the tumor is one with a mixed histologic pattern, and later more extensive microscopic study of the regional lymphatics may show patterns other than those observed in the primary tumor, as was indicated by Dr. Buckwalter.

It is necessary for surgeons to formulate a policy for the management of patients with thyroid cancer. For this purpose, surveys of the sort done by Dr. Buckwalter and his associates and by Dr. Lindsay are helpful. From Dr. Lindsay's survey, one of the important contributions to surgeons was the fact that the malignant thyroid disease often is found in the lobe opposite the one in which the tumor originated. In a rather high percentage of our patients who were studied histologically, i. e., in 25% of the follicular type, in 30% of the papillary type, and in 60% of the undifferentiated lesions, the opposite lobe was invaded by the disease. This points very clearly to the fact that total thyroidectomy is indicated for thyroid cancer.

The authors have stated that palliative removal of the disease to prevent pressure symptoms is worth while, and I agree that all of the thyroid tissue should be removed if possible in such cases.

In order to do total thyroidectomy without damaging the vital structures in the neck, a clean dissection in a surgical field kept free from bleeding is essential. The recurrent laryngeal nerve must be visualized and accurately dissected and, if possible, the parathyroids identified and preserved.

In addition to removal of the regional lymphatics on the side of the primary involvement, the lymphatics on the opposite side should be excised if the other lobe is involved or if the lesion is in the midline.

Another thing about the behavior of thyroid cancer: We have observed, both at autopsy and at operation, that the disease sometimes spreads downward into the mediastinum, either directly or into the substernal lymphatics. Morfit, I believe, indicates that in 6% of his cases such spread had occurred.

We have selected certain patients with cancer of the thyroid for mediastinal dissection, i. e., when the lesions were in the midline or when the lymph nodes beneath the isthmus were found to be involved. In one-half of such cases in which the mediastinum was dissected, cancer was found beneath the sternum. The following lantern slides illustrate the method for removal of the cancer when substernal spread is suspected. [Slides]

We have had a number of patients in whom these more extensive dissections have been done for the removal of thyroid cancer without disfigurement of the patient, and with very little disability from the standpoint of function of the recurrent laryngeal nerves and parathyroids.

Dr. Henry Mason Morfit, Denver: I am very happy to see someone else gather data to substantiate the fact that papillary cancer of the thyroid is a serious disease and does kill people, and that therefore we ought to do something about it.

I am sure you are familiar with the statements made by one of our colleagues from a little further East, in which he compares papillary thyroid cancer to a pimple. He says that if you leave it alone, it won't bother you; but if you prick it it is going to spread all over your body. It spreads all over the body anyway. That is the natural history of this disease, and I congratulate our fellow members on being able to step in and try to do something to keep this from happening.

Dr. Joseph A. Buckwalter, Iowa City: We have wrestled with the criteria useful in the classification of thyroid carcinomas. I am in agreement with the suggestion that, at least from the theoretical point of view, and perhaps from a practical one, the best classification may be on the basis of biologic behavior. However, since relevant information is never complete, it is not always possible to place the lesion in the proper category in this way, either.

At this time I am unable to give you our overall mortality for thyroid carcinoma. These data are being collected. However, there are substantial numbers of patients in our series in whom the diagnosis was confirmed by autopsy done at the University Hospitals who have died of carcinoma of the thyroid.

These or similar data have little statistical significance. Because of the small numbers of cases available for study, it is unlikely that any one investigator will ever arrive at statistically significant differences and conclusions. Therefore, the only hope of finding or reaching firm conclusions concerning the matters discussed is to pool data from several institutions, using similar methods in collecting and examining data.

More than 50% of our poorly differentiated, 15% of our papillary and 20% of our follicular carcinomas have had contralateral spread. Therefore we feel as does Dr. McCorkle, that this is sufficient reason to do a total thyroidectomy for thyroid carcinoma.

How radical should one be in attempting to remove all the carcinoma? The problem seems little different to me than that of carcinoma of the breast, stomach, etc. The type of lesion which Dr. McCorkle's first patient had, an undifferentiated or poorly differentiated lesion, is usually unsuitable for radical surgery in my judgment, because such lesions almost always have already spread beyond limits of excisional therapy. This case proves the exception to this statement.

In concluding, I should like to agree with Dr. Morfit. We have seen patients with papillary carcinoma die of the disease within one and two years of diagnosis.

End-Results in Carcinoma of the Oral Cavity

A Study Based upon Six Hundred Seventy-Nine Cases over a Fifteen-Year Period

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Introduction

At regular intervals it is necessary to analyze end-results in the management of specific lesions in order to adjust treatment policies on the basis of success or failure. The management of carcinoma of the oral cavity is particularly ready for such an analysis because of the past 10 years of intensive attack on these lesions with more radical surgery and irradiation. There is a feeling among many that these intensive measures have not yielded any worthwhile increase in cure rates, while others feel that the radical procedures thus developed should be applied more frequently in earlier situations. The usual partisan appeal of the radiologist and surgeon is even more in evidence than heretofore.

Material

This analysis is based upon a study of 679 cases seen at the Los Angeles County Hospital from 1940 to 1955 inclusive. They were all service cases. The management was in the hands of the house staff, supervised by a visiting attending staff and a full-time head of the department of radiation therapy. There was no limit to the availability of all modern surgical procedures; the department of radiation therapy confined its activities to the use of standard high-voltage radiation and radium. A continuity of follow-up was maintained through the services of the Tumor Board, the members of which were visiting attending men of long tenure. New patients were funneled through a tumor clinic supervised by the full-time radiotherapist and member surgeons of the Tumor Board. All problem cases were reviewed by the Tumor Board. The management of the patients was assumed by the department of radiation therapy or the tumor surgery service.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 21, 1957.

From the Departments of Radiology and General Surgery, College of Medical Evangelists, and the Los Angeles County Hospital.

TABLE 1.—*Location Vs. Five-Year Results*

Site	No. of Cases	Five-Year Results
Lip	152	43%
Tongue *	278	13%
Tonsil	105	2%
Lower gum	44	5%
Upper gum	16	20%
Buccal mucosa	35	30%
Soft palate	31	7%
Hard palate	18	18%

* As explained under "Incidence," this group includes all combined floor-of-the-mouth and tongue lesions.

Incidence

There were (Table 1) 152 cancers of the lip, 105 of the tonsil, and 278 of the tongue. Those of the buccal mucosa, gums, and palate were too few in number to yield detailed information of statistical significance. All floor-of-the-mouth cancers were included in the tongue-cancer group. This inclusion was decided upon when it was noted that over one-third of the tongue cancers were associated to some degree with involvement of the floor of the mouth and vice versa. Otherwise, it would have necessitated the division of this group into three sections: one for tongue, one for floor of the mouth, and one for both areas. Even then the division would have been quite arbitrary and would have been influenced to a great degree by the individual clinical impressions of the initial examiners. It was felt, therefore, that a single grouping of all these patients would yield a series of cases more amenable to significant analysis, without the interference of such ill-defined variables. The 40% incidence of tongue cancer

TABLE 2.—*Untreated Cases*

Site	Percentage Untreated
Lip	15
Tongue	32
Tonsil	30
Intraoral (minus lip)	32

in this group is somewhat higher than that found in comparable groups of cases because of the inclusion of the floor-of-the-mouth lesions.

Cure Rate by Site

Table 1 notes the five year cures obtained in this series of cases in relation to site of origin. Immediately one is impressed by the very low figures, such as the five-year cure rate of 13% for tongue cancer and of 43% for lip cancer. These figures reflect either an inability to manage properly this type of cancer or a very poor selection of cases. A further study (Table 2) shows that almost one-third of the intraoral cancers (excluding those of the lip) and, more specifically, 32% of the tongue and 30% of the tonsil cancers, on admission, were so far advanced that it was not possible to assign definitive curative treatment programs to their management. When the untreated cases are excluded, a reappraisal of the five-year cure rates (Table 3) brings the experience in tongue cancer to 22% and that in all intraoral cancers (minus lip cancer) to 17%. Even these figures are relatively low, but this low cure rate can further be accounted for on the basis of the advanced stage of the disease in those cases that were accepted for definitive therapy. The latter point is emphasized by a review of the tongue-cancer group in relation to survival time (Table 4). Of these patients, 45% were so far advanced that they did not survive six months,

TABLE 3.—*Five-Year Results in Treated Cases*

Site	Five-Year Results	
	Treated	All Cases
Lip	53%	43%
Tongue	22%	13%
Tonsil	3%	2%
Intraoral (minus lip)	17%	11%

and, of this group, 60% were not even amenable to specific therapy. Sixty per cent did not survive one year, and, of these, 50% were untreated.

Tongue Cancer

In order to determine what specific factors could be considered favorable or unfavorable in intraoral cancer, the large group of tongue cancers was analyzed in great detail. As already stated, the over-all five-year cure rate in this group of 278 patients was 13%, and the corrected five-year cure rate for the treated cases was 22%.

TABLE 4.—*Survival Time for Tongue Cancer*

Duration	Percentage	Untreated, %
Less than 1 mo.	18	80
Less than 6 mo.	45	60
Less than 12 mo.	60	50
Less than 2 yr.	80	40
2 to 5 yr.	10	
5 to 10 yr.	9	
10 to 13 yr.	1	

In order properly to evaluate the importance of each of the factors noted in Table 5, they were analyzed from the standpoint of absolute incidence, and relatively by comparison with each other. In this manner, it was felt that the many variables resulting from a selection of favorable cases in each group would be more nearly equalized.

Sex.—Of this group 20% were female. This is about double the incidence of females noted in earlier studies. The over-all five-year cure rate for this group was 24%, as against 13% for the entire group. The main difference between the female group and the entire series was a 13% higher incidence of primary lesions over 3 cm. in diameter. Otherwise the groups were quite comparable. From this analysis one is forced to conclude that the more favorable results obtained in this group can in great measure be accounted for by the fact that female patients report for treatment with earlier (smaller) primary lesions.

Color.—Non-Caucasians, mostly Negroes, made up 8% of the group, and their five-year cure rate was 9%. This is almost 33%

TABLE 5.—*Factors Influencing End-Results (Tongue Cancer)**

	Five-Year Results	(Incidence)
Females	24%	(20%)
Non-Caucasian	9%	(8%)
Under 50 yr	10%	(16%)
Syphilis	7%	(22%)
Primary over 3 cm.	7%	(62%)
Location at base	0%	(20%)
Involved nodes	5%	(78%)
Bilateral	0%	(20%)
Distant metastases	0%	(7%)

* Over-all five-year cure rate for 278 patients with tongue cancer was 13%.

lower than the over-all experience. Here, however, the primary lesions over 3 cm. and the numbers of cases with metastases in the cervical lymph nodes were 13% and 12%, respectively, higher than in the entire group. The poorer results might therefore again be attributed to the neglect of this group to report for treatment until the disease was far advanced.

Age.—It was noted that the patients under 50 years of age, with an incidence of 16%, had a five-year cure rate of 10%. This was slightly less than the rate for the over-all group, but when compared with the figure for the over-50 age group the difference was of more significance. This under-50 group had fewer primary lesions over 3 cm. in diameter and 12% more cases with positive cervical lymph nodes. There were more female patients and less syphilis in this group, both favorable factors. Also, the higher incidence of lymph node involvement might be due to the greater tendency of this group of cancers to metastasize, in spite of the fact that it contained more early or smaller primary lesions. It would appear, therefore, that patients under 50 years of age have a poorer prognosis than those over 50.

Syphilis.—Because of the frequency with which syphilis is associated with carcinoma of the tongue, the relationship was investigated from the standpoint of prognosis. In this series there was an incidence of syphilis of 22%, with a five-year cure rate of 7%. This is about one-half as good as that for the entire group. A break-down of the favorable and unfavorable factors in this syphilitic group revealed primary carcinomas over 3 cm. and lymph node metastases to be 15% and 10% higher, respectively, than the figures for the group as a whole. There were fewer cases with distant metastases and patients under 50 years of age and a higher percentage of female patients and non-Caucasians. In balance, it seemed as though the advanced stage of the disease in the syphilitic group was mainly responsible for the poorer prognosis, but whether these two factors were in direct relationship was difficult to ascertain.

Clinical Factors.—From a clinical standpoint it was almost certain that the more advanced lesions would have a poorer prognosis. In this analysis this presumption was verified. The larger primary lesions over 3 cm. occurred in 62% of this series and had a five-year cure rate of 7%, about one-half that for the group as a whole. That this poor result was not due to any other major factor is shown by an analysis of the variables previously mentioned. They all are comparable to the same factors in the group as a whole, with the exception of a 7% increase in lymph node involvement.

When the primary lesion was located at the base of the tongue (20% incidence), the five-year cure rate was zero. Here the unfavorable associated factors involved were the large size of the primary lesion, which occurred 17% more frequently; lymph node metastases, which were 6 per cent as frequent, and distant metastases, which were two and one-half times as frequent. Although the advanced stage of these base lesions was a primary factor in the poor prognosis, it was felt that this location per se was associated with a greater tendency toward more extensive local growth and wider dissemination. This assumption is further verified by an analysis of the grade of the tumor, which in this location revealed a 60% incidence of Grades 3 and 4, as against an experience of 30% in the group as a whole.

Lymph nodes were positive for metastatic carcinoma in 78% of the entire group, with

TABLE 6.—*Five-Year Results Vs. Staging (Tongue Cancer)**

Total No. Cases	Stage	Five-Year Results
17	Primary only	68%
60	Primary over 3 cm. in diameter (with or without involved nodes)	12%
75	Node involvement at any time	7%
18	Bilateral node metastases	0%

* Over-all five-year cure rate for treated patients was 22%.

a five-year cure rate of 5%. When the involvement was bilateral (20% incidence), the cure rate was zero. An analysis of all the determining factors revealed them to be reasonably comparable to the group as a whole. Therefore the poor prognosis here is directly related to the presence of metastases in the cervical lymph nodes.

Stage.—As previously noted, the over-all five-year cure rate for carcinoma of the tongue in the treated cases was 22%. In the group with only primary disease the five-year cure rate was 68% (Table 6), but when lymph nodes were involved at some time during the entire period, the five-year cure rate equaled 7%. If the treated case had a primary lesion over 3 cm., with or without node metastases, the five-year cure rate was 12%. There were no five-year cures with bilateral lymph node involvement.

Method of Treatment

The crux of the entire problem was to determine whether one method of management was superior to the others. An analysis of the treated cases on the basis of modalities used (Table 7) revealed that the highest five-year cure rate, of 42%, was obtained in that group of cases treated by a combination of surgery and irradiation.

TABLE 7.—*Five-Year Results Vs. Method of Treatment (Tongue Cancer)**

Total Cases	Type of Treatment	Five-Year Results
46	Irradiation alone	15%
34	Surgery alone	21%
19	Surgery+irradiation	42%
27	Radical neck dissection (including "commando")	30%
14	"Commando" procedure †	21%

* Over-all five-year cure rate for treated cases is 22%.
† Combined intraoral excision, mandibulectomy, and radical neck dissection.

Surgery alone yielded a 21% five-year cure rate, whereas irradiation alone yielded a 15% five-year cure rate. This finding is not paradoxical, since it has always been recognized by the therapists in this field that carcinomas of the mucosal surfaces of the head and neck require the use of both modalities in their management. Furthermore, these modalities are not competitive, but have very specific indications for their use. To achieve the best results, it has long been accepted that the head-and-neck-cancer therapist must individualize the management of each and every patient; he must decide whether surgery or irradiation or both is indicated, and, if both, in what sequence.

Neck Dissection

A further analysis of the surgical procedures used revealed that the cases of tongue carcinoma which also had radical

TABLE 8.—*Results in Neck Dissection (Tongue Cancer)*

Total Cases	No. of Cases and Status	Three-Year Results
51	All positive and negative nodes	37%
41	Positive nodes	24%
16	Elective positive nodes	37%
25	Therapeutic positive nodes	16%

neck dissections had a five-year cure rate of 30%. A further break-down on a three-year basis (Table 8) revealed that those cases having positive nodes had a cure rate of 24%. When these positive nodes were discovered in elective (prophylactic) neck dissections, the cure rate was 37%, but when found in therapeutic neck dissections, the cure rate was 16%. These figures are based upon an analysis of rather small groups of cases; but if the trend revealed so far continues, it will establish statistically the value of radical neck dissection in the management of carcinoma of the tongue, particularly if it is performed as an elective (prophylactic) procedure.

"Commando" Procedures

The more radical "in-continuity" operations, commonly referred to as the "com-

mando" procedure, as performed in this series for tongue cancer, yielded a five-year cure rate of 21%. If the removed lymph nodes were positive for metastatic involvement, the five-year cure rate dropped to 8%. This group of cases had several very favorable factors to its advantage, namely, primary lesions over 3 cm. in only 48% of the cases, as against a group experience of 61%, and no base-of-the-tongue lesions, as against 20% for the entire group. This series, of 23 cases, is too small to warrant a more detailed analysis of the factors involved. It is felt that the operation is too often used as a last resort in nonresectable situations and in the very limited case, where it is not indicated. This series is, as yet, not large enough to yield statistically significant answers to the questions of indication for and value of the "commando" procedure. We hope to have more definite answers in a later review. That this operation has a place in the management of carcinoma of the tongue is not doubted, but what that place is has as yet not been determined.

Conclusions and Summary

The cure rate in carcinoma of the oral cavity is dependent upon the type of management and the selection of cases.

At the Los Angeles County Hospital the over-all five-year cure rate was 11%. This was due to a poor selection of material, as evidenced by the inclusion of 32% of cases which were so far advanced as not to be eligible for definitive therapy. If the untreated cases were excluded, the five-year end-result rose to 17%.

A more detailed analysis of carcinoma of the tongue (including floor-of-the-mouth cancers) revealed an over-all five-year cure rate of 13%. When the untreated cases were eliminated, the five-year cure rate equaled 22%.

By analyzing the variable factors involved in carcinoma of the tongue, it was found that the best results would be obtained in a white woman over 50 with only a primary lesion, under 3 cm. in diameter, in the anterior two-thirds of the tongue, which is treated by a combination of surgery and irradiation and elective neck dissection.

Surgery and irradiation are indispensable in the management of carcinoma of the oral cavity. They are not competitive. The case must be individualized by the proper selection of the indicated modality or by a combination of modalities, and, if the latter, in the proper sequence.

Treatment must be complete and all-encompassing at the time of the initial management. This should result in ever-increasing cure rates, as intraoral carcinoma can easily be detected and remains localized above the clavicle in about 90% of the cases.

300 S. Beverly Dr., Beverly Hills, Calif. (Dr. Perzik).

Cancer of the Stomach

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It is obvious in a critical comparative survey of the literature on gastric carcinoma that there is a wide variation in the published five-year survival rates. Thus, the reported rates expressed in terms of five-year survivors range from a low of 0.7% to a high of 35%.[1-4,6,8,9] Some of the factors causing this marked disparity, such as differences in methods of reporting results are evident. Other factors, such as the involuntary selection which occurs as a result of the inherent nature of the institution reporting its data, are subtler.

The present study provides a rather unique opportunity to compare the results in patients with gastric carcinoma treated in three widely different types of institutions: a Government institution, represented by the Veterans' Administration Hospital, Dearborn, Mich.; a city institution, represented by the Receiving Hospital of the City of Detroit, and a private hospital, represented by the two units of the Grace Hospital, Detroit. In addition, there are certain constant factors in two of the hospitals—the Dearborn Veterans' Administration and the Detroit Receiving Hospital, for they are both under the professional direction of the surgery department of Wayne State University College of Medicine and both have the same resident and consulting staff. The principles of cancer surgery are therefore similar; and, as a matter of fact, the general operating technique is rather standardized.

This survey includes all cases of adenocarcinoma of the stomach initially treated in these three institutions over a 10-year period beginning Jan. 1, 1946, and ending Dec. 31, 1955. Only those cases were included in which the lesion was histologically proved to be gastric carcinoma at operation or autopsy, except in a very few instances in which gastroscopic examination confirmed the x-ray diagnosis.

TABLE 1.—*Sex Distribution of 637 Patients with Carcinoma of the Stomach, in Three Hospitals*

	Receiving No.	Veterans' Admin. No.	Grace No.	Total No.	Total Per Cent
Sex					
Male	129	137	207	473	75
Female	48	0	116	164	25
Total	177	137	323	637	

There was a total of 637 patients: 177 at the Detroit Receiving Hospital, 137 at the Dearborn Veterans' Administration Hospital, and 323 cases at the Grace Hospitals (Table 1). Approximately two-thirds of each series were men, except at the Veterans' Administration Hospital, where all patients are men.

In 393 of the entire 637 cases under consideration, the diagnosis was made on operation performed more than five years ago (January, 1946, to March, 1951). Through the efforts of the Tumor Boards of the various hospitals and the Department of Vital Statistics in Lansing, Mich., a successful follow-up was attained in 94% of cases at the Dearborn Veterans' Hospital, in 87% at the Detroit Receiving Hospital, and in

TABLE 2.—*Successful Follow-Up in Series of 637 Cases of Carcinoma of the Stomach, in Three Hospitals*

	Receiving	Veterans' Admin.	Grace	Total
Total cases	94	91	208	393
Successful follow-up	82	86	184	352
Lost to follow-up	12	5	24	41
% successful follow-up	87	94	88	90

Clinical Fellow in Surgery, American Cancer Society (Dr. Koucky).

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 21, 1957.

TABLE 3.—*Absolute Five-Year Survivals*

	Receiving	Veterans' Admin.	Grace	Total
No. cases	94	91	208	393
No. survivals	1	12	20	33
% survivals	1	13	10	9

88% at the Grace Hospitals (Table 2). Considering the nature of the institutions, this percentage of follow-up is considered excellent, and the difference in the percentages of patients lost to follow-up in the three groups is not large enough to affect materially the final survival rates. In computing five-year survival results, all persons lost to follow-up were presumed to be dead.

Of the 393 patients having a chance to live five years, 33 are living and well, without evidence of recurrence at the present time, resulting in an absolute five-year survival rate of 9% (Table 3). Comparison of the figures at the three institutions, however, shows widely varying results, with 1, 12, and 20 patients surviving five years or more at the Receiving Hospital, Veterans' Administration Hospital, and Grace Hospitals, respectively. This results in a 1% absolute survivorship at the Receiving Hospital, 13% at the Veterans' Administration Hospital, and 10% at the Grace Hospitals.

Considering the number of patients surviving, of those undergoing resection with hope of cure, there is a 43% survival rate at the Veterans' Administration Hospital, which compares favorably with the best results in the country [3,9,10]; a 3% survival rate at the Detroit Receiving Hospital, which duplicates the worst results in the country, and a 21% rate at the Grace Hospitals, which occupies an intermediate position [2,5,8] (Table 4).

A "resection for cure" in this series refers to an operation, regardless of the extent, in which the operating surgeon was of the opinion that all grossly carcinomatous tissue had been removed. A "palliative resection" is one in which obvious cancer has been left behind. The classification of a curative or palliative operation was based on reviewing the surgeon's operative dictation, and, since the same observers reviewed all the charts with the same goal in mind, the comparative results are apt to be of some significance.

TABLE 4.—*Five-Year Survivals of Patients Undergoing Resections for Cure*

	Receiving	Veterans' Admin.	Grace	Total
No. cases	32	28	92	152
No. survivals	1	12	20	33
% survivals	3	43	21	21

In an effort to explain the marked variation in survivors, we have carefully analyzed our material and shall present only those data which we believe to be important in explaining the differences. Figure 1 shows that we are dealing with slightly different age groups in the three institutions and that the largest number of patients in the

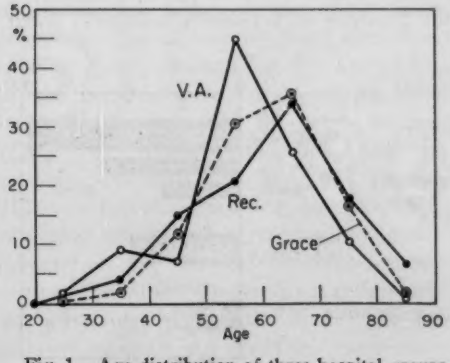

Fig. 1.—Age distribution of three hospital groups of patients with carcinoma of the stomach.

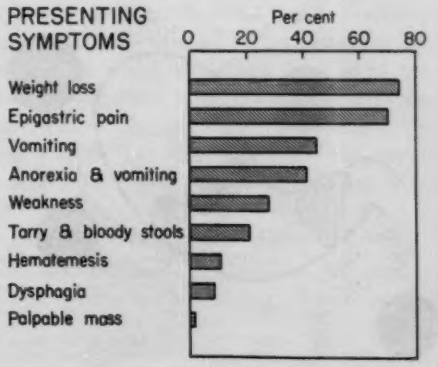

Figure 2

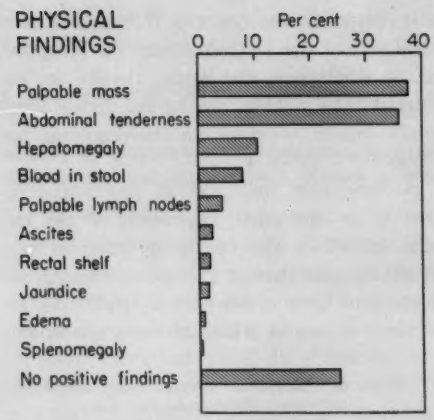

Figure 3

Receiving Hospital series occurs in the seventh decade of life, whereas at the Veterans' Administration Hospital the largest number was in the sixth decade, with the Grace Hospital group occupying an intermediate position. Although this does not explain differences in the stages of the disease, it suggests that the Receiving Hospital is dealing with an older population, where possibility of surviving may be expected to be less. This factor is particularly significant in this series, for no distinction was made between death from carcinoma and death from an unrelated cause within the five-year period.

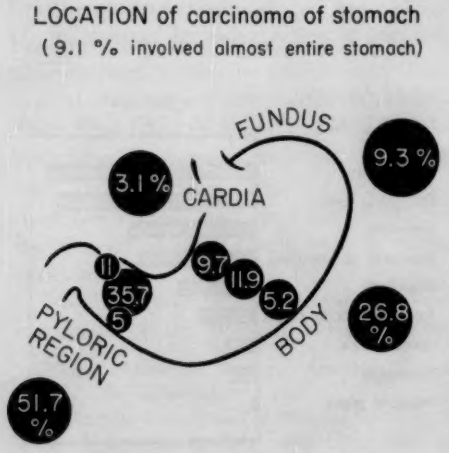

Figure 4

With one exception, the presenting symptoms were fairly uniform in all three hospitals, the commonest complaint being that of weight loss, followed by epigastric pain, vomiting, anorexia, weakness, tarry or bloody stools, hematemesis, dysphagia, and, finally, a palpable mass (Fig. 2). Although 74% of the entire group complained to some degree of weight loss at the time of admission, conforming with other published reports,[1-5] this symptom was more marked in the Receiving Hospital patients, in that it occurred in 84%, while in the Veterans' Administration and Grace Hospitals it occurred in 70%. In addition, 16% of the patients in the Receiving Hospital lost 50 lb. or more before admission, while only 8% in the other two groups lost so much.

The commonest physical finding at the time of admission was the presence of a palpable abdominal mass, presumably due to the gastric malignancy (Fig. 3). This occurred in 34% and was followed, in decreasing order, by abdominal tenderness, hepatomegaly, melena, palpable lymph nodes, ascites, rectal shelf, jaundice, edema, and splenomegaly. It is interesting to note that 25% of the patients had no positive physical findings whatever at the time of their admission to the hospital. Of even more significance is the fact that only 16% of the patients at Receiving Hospital presented themselves with negative physical findings, while at the Grace Hospital this figure rose to 25% and at the Veterans' Administration Hospital to 36%. Likewise, the presence of a palpable mass was noted

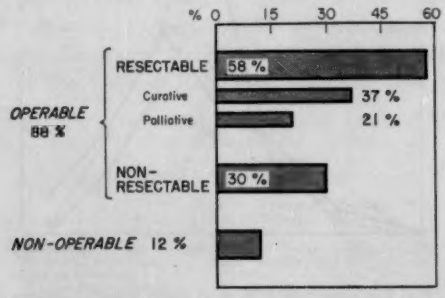

Figure 5

TABLE 5.—*Local Extension of Tumor: Curative Resections*

	Receiving	Veterans' Admin.	Grace
To serosa	48%	70%	65%
Through serosa	52%	30%	35%

in almost one-half of the Receiving Hospital series, while only one-quarter of the Veterans' Administration patients and one-third of the Grace Hospital patients presented themselves with a mass in the abdomen. These findings indicate a more extensive malignant process in the city hospital group than in the Veterans' Administration and private hospital series and correlate closely with the survivor figures.

No significant differences were found in the locations of the carcinoma of the stomach (Fig. 4). The figures in the larger circles in Figure 4 indicate the percentages of malignancies located in the major divisions of the stomach, 9.1% involving almost the entire stomach. The body and pyloric regions are further subdivided to indicate the location of the lesion on the lesser or the greater curvature, the central figure indicating those tumors which involve both curvatures. It is interesting to note that approximately 50% of the carcinomas in all three series occurred in the distal third of the stomach.

Our over-all operability rate of 88% is high as compared with other published reports [1-3,6-8] and probably reflects our inclusion in this series of only those cases proved histologically or by direct inspection to be of gastric cancer (Fig. 5). Only 12% of the patients were considered to have inoperable cancer. Of the total number (637) under consideration, 58% had resection—37% with some hope of cure and 21% as a palliative procedure only. In 30% operation was done but resection could not be carried out because of far-advanced disease. There are no significant differences in operability among the three hospital groups except in resection for cure or palliation. Here the Receiving Hospital group showed fewer operations for cure (28%) than for palliation (31%), whereas the Veterans' Administration and Grace Hospitals both showed many more resections for cure (44%) than for palliation (16%). Again, this would indicate a more advanced disease in the city hospital group than in the Veterans' Administration group or in the private hospital series and explains somewhat the differences in survival figures.

Furthermore, in 52% of the curative resections in the Receiving Hospital group, tumor had extended through or beyond the gastric serosa, while this was true in only 30% of the Veterans' Administration group and in 35% of the Grace Hospital groups. Histologically positive lymph nodes were found in 62% of the curative resections in the Receiving Hospital series, while this was the case in only 47% of resections in the Veterans' Administration patients and in 57% of the Grace Hospital patients (Tables 5 and 6). This difference demonstrates that even in those cases in which the surgeon was resecting with the intent of cure the disease was further advanced in the city hospital cases.

Quite obviously, the operative mortality might affect survivorship in that the higher the mortality the fewer would be patients having a chance to live the five-year period. In this series an operative mortality denotes the death of a patient from any cause within 30 days of the operation or at any time interval if the death can be attributed to complications of surgery.

The term distal subtotal gastric resection refers to the standard radical subtotal resection, in which the distal portion of the stomach together with both omenta is removed and the proximal portion of the stomach is anastomosed with the small bowel. The over-all operative mortality

TABLE 6.—*Lymph Node Metastases: Curative Resections*

	Receiving	Veterans' Admin.	Grace
Negative lymph nodes	38%	53%	43%
Positive lymph nodes	62%	47%	57%

TABLE 7.—*Operative Mortality for Subtotal Distal Gastric Resection*

	Receiving	Veterans' Admin.	Grace	Total
Performed	75	51	152	278
Deaths	7	4	20	31
Mortality rate	9%	8%	13%	12%

TABLE 8.—*Operative Mortality for Subtotal Proximal Gastric Resection*

	Receiving	Veterans' Admin.	Grace	Total
Performed	8	3	14	25
Deaths	2	1	6	9
Mortality rate	25%	33%	43%	36%

from such a procedure was 12%, being 9% at the Receiving Hospital, 8% at the Dearborn Veterans' Administration Hospital, and 13% at the Grace Hospital (Table 7).

A proximal subtotal gastric resection denotes the removal of the upper portion of the stomach, with the anastomosis of the esophagus to either the distal portion of the stomach or to the small bowel. The over-all operative mortality of this procedure was 36%, being 25% at Receiving Hospital, 33% at the Veterans' Administration Hospital, and 43% at the Grace Hospital (Table 8).

The operative mortality for total gastrectomy was 44%, being 55% at the Receiving Hospital, 35% at the Veterans' Administration Hospital, and 40% at the Grace Hospital (Table 9).

Although there are slight differences in the operative mortality in the three hospitals, close analysis reveals that this in itself would not explain the differences in survivor rates. The mortality for the proximal subtotal and total gastrectomy is unusually high in all three hospitals, indicating the poorer anastomosing qualities of the esophagus, and perhaps reflects the philosophy of performing a total gastrectomy not as a routine measure for the treatment of gastric cancer but as an effort to remove all carcinoma in cases of far-advanced malignancy.

TABLE 9.—*Operative Mortality for Total Gastrectomies*

	Receiving	Veterans' Admin.	Grace	Total
Performed	20	17	20	57
Deaths	11	6	8	25
Mortality rate	55%	35%	40%	44%

Summary and Conclusions

There exists in the Detroit area an excellent oportunity of comparing survival rates of cancer of the stomach in three widely different types of institutions: a city, a Government, and a private hospital.

The series is somewhat unique in that (*a*) the same observers have reviewed all the cases, making the results somewhat constant, and (*b*) the operating teams are the same in two of the hospitals.

It is shown that the results in carcinoma of the stomach are not nearly as discouraging as many previous reports would indicate, since this series shows an over-all absolute five-year survival rate of 9%, with a 21% five-year survival rate among those undergoing resection with any hope of cure.

The number of patients with resection for cure who are living and well without evidence of recurrence for five years is excellent in the Veterans' Administration Hospital, being 43%, and is extremely poor in the City of Detroit Receiving Hospital, where it is 3%, with the private institution occupying an intermediate position, with 21%.

It has been shown that a difference in the condition of the patient and the extent of his disease is largely responsible for the difference in survival rates at these three hospitals.

It is suggested that these same differences may account for many of the variations in other reported series rather than differences in operations, technique, or ability of the surgeon.

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Combined Abdominoendorectal Resection for Lesions of the Mid and Upper Parts of the Rectum

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A procedure of the pull-through type, called descriptively a combined abdominoendorectal resection, has been used in the surgical service of one of us (B. M. B.) since 1948. It differs from the usual sphincter-saving operation in that the most distal 3 to 4 cm. of rectum is preserved instead of the sphincter only. While the technical modification is relatively minor, subsequent fecal control is thereby improved greatly. Experience (through 1956) with the procedure in the treatment of 106 patients with carcinoma, 5 with benign polypoid lesions, 2 with megacolon, and 1 with segmental chronic ulcerative colitis forms the basis for the present report.

Technical Considerations

The technical aspects of the operation have been described in detail previously,[3,4] and only certain features and changes that have been made in the technique will be considered at this time. The abdominal part of the procedure is identical with that of sphincter-saving operations, except that a heavy ligature is tied around the rectum below the lesion to prevent soiling from above during the subsequent endorectal part. Closure of the pelvic peritoneum after packing the previously mobilized bowel into the pelvis may be difficult or impossible. The problem arises particularly in cases in which the pelvis is small, the peritoneum is involved extensively, the lesion is large, or the amount of fat on the wall of the bowel is excessive. In such cases, formerly, to reduce the amount of bowel to be packed into the pelvis, a segment of mobilized bowel was resected. The two ends of the bowel were then closed and tied together. We have now largely abandoned the practice, preferring instead merely to pack the bowel into the pelvis, without attempting to form a new pelvic peritoneal diaphragm. So far, in some 10 cases, no complications resulting from failure to reperitonealize have occurred.

The endorectal part of the procedure is relatively minor. After dilation of the sphincter, the short segment of rectum, limited above by the previously placed ligature, is cleansed. The portion of the wall of the rectum constricted by the ligature is grasped by a hemostat, and, by gentle traction, the rectum is inverted. A circular incision is then made through the entire thickness of the rectal wall at the selected level, usually 3 to 4 cm. above the dentate margin. The previously mobilized bowel is pulled carefully through the anorectal canal until viable bowel protrudes well beyond the anus. This segment of bowel, in which the lesion is of course situated, is excised, leaving a short length protruding beyond the anus. Retraction of the colon is prevented by suturing epiploic tags to the perianal skin.

Healing between the upper cut end of the rectal stump and the serosa of the colon is usually sufficiently advanced after two weeks to permit the trimming back of the colon to well above the level of the

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sphincter. Before the bowel is trimmed back, the union between rectum and colon should be examined carefully. If healing has not occurred around the entire circumference, removal of the redundant bowel should be postponed until healing has occurred.

What has been achieved to this point is essentially a colonic stoma opening into the stump of rectum. Subsequent developments are similar to those that occur after the formation of an abdominal colonic stoma. Local edema, particularly of the wall of the colon, regresses slowly. The epithelium of the rectum grows toward and ultimately meets that of the colon. The cut end of the colon usually everts somewhat, thereby shortening the distance between the two layers of epithelium. During the healing process, which may take several months, there is always some narrowing of the stoma, so that an occasional finger dilation is advisable. Attempts have been made repeatedly to hasten healing by suturing endorectally the cut end of the colon to the mucosa of the rectum. The procedure is comparable to the minor plastic procedures occasionally carried out to speed the maturation of an abdominal stoma. As in the case of abdominal stomas, the maneuver does not seem to influence fundamentally the course of healing or to improve the anastomosis achieved ultimately.

In some cases, particularly if dilations have not been carried out, the cut end of the colon tends to constrict rather than to evert. A buttonhole type of stricture, sufficiently tight to produce symptoms, may form in time. Such strictures, which are never dense, may be easily and safely dilated, since they involve the end of the colon only and not the actual anastomosis. The dilations usually do not require anesthesia and may be done as an office procedure. Strictures of this type do not tend to re-form, and late stricturing, such as that which occurs at the level of the skin after abdominal stomas, has not been seen after endorectal procedures.

Complications

The complications more or less characteristic of pull-through procedures are sloughing of the pulled-through bowel and the formation of abscesses in the pelvis. Considerable progress has been made during the past year or so in the prevention of both.

Sloughing of Colon.—Some sloughing of the colon occurred in 21 of the 114 cases in the series. In 17 cases the slough did not extend above the upper end of the rectal stump, and the only consequence was that the bowel did not have to be trimmed back above the sphincter. In four cases (3.5%), however, sloughing did extend high enough to disrupt continuity of the bowel, leading to the formation of fecal abscess, fed by the colon, above, and drained through the anorectal canal, below. Colonic stomas were established in three cases, while in the fourth the complication was managed conservatively.

In an effort to prevent sloughing, we have recently changed our practice with respect to the division of the inferior mesenteric artery. Formerly, the artery was divided at the aorta. Our experience was similar to that of Goligher, who found the arterial supply of the descending colon to be inadequate in 5 of 37 cases. We now perform a clean dissection of the artery from its origin to below the left colic artery or, in its absence, to below the first sigmoidal branch. The artery is occluded temporarily, and the adequacy of the remaining circulation to the upper sigmoid and descending colon is determined before the artery is divided. If the arterial supply is doubtful, the vessel is divided below the first branch. We are, in fact, tending increasingly toward this practice. Since the areolar tissue and nodes are removed completely during the dissection, there is little likelihood that involved nodes in the region will be left behind.

Although we hope that the incidence of sloughing can be reduced by the formal preservation of the left colic artery, we are

somewhat pessimistic that the complication can be avoided entirely. As judged from the literature, sloughing has occurred in spite of all precautions.[1,14] Sloughing has occurred in cases in the present series in which there could be no doubt that the circulation was adequate at the conclusion of the operation. The infarction of the bowel in such cases undoubtedly results from thrombosis of the marginal artery during the immediate postoperative period, probably as a result of trauma to the vessel, or as a consequence of an interval of hypotension. It is, of course, possible that thrombosis may be prevented by preserving a more vigorous arterial flow.

Pelvic Abscesses.—Pelvic abscesses not the result of sloughing of the colon developed in 10 cases in the series. Although such abscesses provoke surprisingly little systemic reaction, they are most troublesome in that they always prolong convalescence. Complete healing between the colon and the rectum may be delayed greatly, and fistulas between the bowel and the perineum or vagina may develop. Occasionally a blind sinus leading from the anastomosis into the space in the hollow of the sacrum persists for many months. The abscesses were so indolent in two cases in the series that temporary colonic stomas were established to speed their resolution.

In the absence of sloughing or gross soiling, pelvic abscesses usually result from a collection of serum in the dead space in the pelvis. In an effort to provide more efficient drainage, suction by means of a catheter inserted through the perineum was substituted early in 1956 for the Penrose drains previously used. As much as 300 to 400 ml. of serum is usually recovered during the first 24 hours. The amount decreases progressively until, by the fifth or sixth day, it becomes negligible. The catheter is then removed. This method of drainage seems to have virtually eliminated the complication. In none of the 23 patients in the series so treated did abscesses develop. Minor abscesses developed in two patients treated during 1957 (not included in the present series). Far less than the usual amount of serum was recovered in both. It is, of course, obvious that the serum must be removed if the abscess is to be prevented.

Failure of Union Between Colon and Rectum.—It is our custom to divide the colon approximately 2 to 3 cm. below the level of the junction of the cut end of the rectum with the colon. If this is done as early as two weeks after the first stage, there is always some retraction. The end of the colon usually retracts to about the level of the cut end of the rectum. If the trimming back is delayed for three weeks or longer, the tendency for the bowel to retract is much less. However, to speed convalescence, we usually trim the bowel after about two weeks.

Retraction of the end of the colon to a level above the upper limit of the rectal stump occurred in two instances in the series. The first instance was in the first case of megacolon in an adult treated by the method. (In the other case of megacolon in the series, the protruding colon was left in place for six weeks. After this interval the bowel seemed firmly fixed in place and showed no tendency to retract.) Healing was delayed in the second instance by bleeding from raw surfaces in the pelvis. The patient had an unusual clotting defect, not recognized before operation. In both patients intestinal continuity was reestablished by suturing endorectally the colon to the rectal stump, and both ultimately regained fecal control.

Late Stricturing.—Late stricturing of the anastomosis developed in three of the four cases of high sloughing. Stricturing would in all probability have developed in the fourth case had the patient survived. The two patients who survived the establishment of a colonic stoma were left with a rectal pouch, occluded above by dense scar tissue. It was thought inadvisable to attempt to reestablish intestinal continuity in both cases. The fecal abscess in the third case was al-

lowed to run its course. As the abscess slowly but steadily decreased in size, the end of the colon was drawn down to that of the rectum by dense scar tissue, which contracted ultimately to produce obstruction. The lumen was restored by partial endorectal excision of the mass of scar tissue. While there is still much scarring in the region, the lumen has remained adequate for a period of some three years.

Colonic Stomas.—Colonic stomas, as mentioned previously, were established in five cases. The stomas established because of sloughing were considered as permanent, while the two established because of infection and hemorrhage were closed subsequently. The necessity of forming a permanent stoma defeats, of course, the purpose of the procedure. Even if the stoma is to be temporary, the procedure is associated with some risk and increases greatly the period of hospitalization and postoperative morbidity. If sloughing and pelvic abscesses could be prevented, the need for a proximal stoma would practically never arise.

Hospital Deaths.—Only one of the complications in the series resulted in the death of the patient. The death resulted from pulmonary embolism, which occurred after a colonic stoma established because of a pelvic abscess. There were five other hospital deaths among patients in the series, none of which, however, could be attributed to the type of procedure employed. Two resulted from pseudomembranous ulcerative ileocolitis, and one each from peritonitis and hypertensive congestive heart failure. In the fifth case permission for necropsy could not be obtained. Death was thought to have resulted from mesenteric thrombosis.

As judged from the present series and those of Bacon [1] and of Waugh and coworkers,[13,14] who have reported hospital mortality rates of 3.9% and 3.6%, respectively, the risk of pull-through procedures is comparable to, but not less than, that of combined abdominoperineal resection. This is disappointing and was somewhat unexpected, since pull-through procedures are far less extensive than combined abdominoperineal resection. Blood loss and shock are materially less, and the procedure is more quickly completed. It would seem that with either type of operation postoperative deaths result from more or less unavoidable medical or surgical catastrophes.

Fecal Control

The renewed interest in preserving continence after resection of lesions of the rectum has led to the reinvestigation of the mechanism of normal fecal control. Gaston's work is probably the most comprehensive in the field.[7,8] Normal control may be described briefly as follows: Stool is accommodated in the left portion of the colon by a process of gradual enlargement. To a certain extent the colon adapts itself to its contents without producing any sensation. Distention of the colon ultimately produces a sensation of gas or of fullness referred to the left iliac fossa or lower part of the abdomen and also stimulates peristalsis, which ejects the mass into the rectum. The distention of the rectum leads to relaxation of the internal sphincter and a prompt contraction of the external sphincter, sufficient to prevent soiling. Distention of the rectum also gives rise to a desire to defecate (rectal sensation), referred to the presacral region or perineum. The desire to defecate gradually diminishes as the rectum dilates to accommodate its increased contents. As the pressure in the rectum falls, the tone of the sphincter returns to the resting level. Gaston [7] found that the average maximal contraction of the sphincter was 44 cm. of water, and that the average maximal time of contraction was 53 seconds. The strength of contraction of the sphincter may, of course, be reinforced voluntarily, but its original increase in tone, together with dilatation of the rectum, on which control is dependent, is reflex in nature.

After sphincter-saving procedures in which the rectum is removed completely,

normal fecal control is, by definition, lost completely. In such cases what Gaston has termed "reservoir continence" is preserved, and, of course, the sphincter has tone and can be contracted voluntarily. It is surprising, in view of the complete absence of rectal sensation and of a distensible rectum, how well many patients do. Waugh and coworkers [14] reported that 10% of patients considered control to be as normal as before the operation. In 42% of cases, nondiarrheal stools were controlled completely and no perineal pad was necessary. Pads were necessary, however, in 46% of cases, and in somewhat more than 20% of cases only what the authors considered as a perineal colostomy was achieved. Bacon reported that in some 40% of cases complete movements were achieved without irrigations, while in 60% of cases continence was achieved by means of regular irrigations.

Since both rectal sensation and a distensible rectal pouch are preserved, fecal control should be essentially normal after endorectal resection, provided that a sufficient length of rectum is preserved and that the preserved rectum and sphincter function normally. Of the 108 surviving patients in the present series, 1 had a colonic stoma before operation, and in 2 cases stomas were established postoperatively. We have been unable to determine the status of fecal control in four cases. In 93 of the remaining 101 cases essentially normal fecal control was achieved in that the patients did not soil themselves, wear pads, or follow any type of colostomy program. Several patients in the group, who regard their fecal control as normal, have resumed their former enema or cathartic habits, but this was not done to improve fecal control.

The other eight patients, for practical purposes, are incontinent. Fecal control in four senile patients was somewhat faulty before operation. In each it was impossible to keep the perianal region clean and dry postoperatively, and ultimately the entire area became extensively inflamed. The sphincter has remained incompetent in each, leading to continuous soiling, which, in turn, keeps the perianal skin continuously inflamed. The course of events is quite typical, and even predictable. Faulty control in two cases was clearly the result of local recurrence of the lesion, while in another case the sphincter has never regained its tone. The reason for this is not evident, since the patient is not elderly and can contract the sphincter at will. In the final patient without control, far less than 3 cm. of rectum was saved. The fecal control achieved by the patient resembles that after sphincter-saving procedures.

Comment

A series of investigations of the spread of carcinoma of the rectum, beginning with that of McVay and continuing virtually to the present, provides the pathologic basis for pull-through procedures. Retrograde spread, either in the wall of the bowel or through lymphatics, is unusual and practically never extensive in operable patients. Best and Blair, for example, in a series of studies of 600 specimens reported in the literature, said that retrograde spread more than 2 cm. below the lower limit of the lesion had been found in less than 1% of cases. Lateral spread becomes increasingly rare the higher the lesion is situated above spread has not been found in operable cases the dentate margin. While lateral lymphatic in which the lesion was higher than 4 cm., it has been found with lesions the lower margin of which is below that level.[6,11] Consequently, the proper management of lesions of the lower third of the rectum, or those within 5 to 6 cm. of the dentate line, implies removal of the lateral zone of spread, including the levators and sphincter.

In the treatment of lesions above the lower third of the rectum it would appear safe to preserve these structures, provided that a safe margin of bowel and perirectal lymphatics are removed below the lesion. It is now agreed that probably 5 cm. of apparently uninvolved bowel below the lesion, as measured before resection, does

provide a safe margin. The removal of bowel above the lesion and the proximal zone of lymphatic spread needs no particular comment, since it is the same whether a pull-through or a combined abdominoperineal resection is carried out.

Parenthetically, pull-through procedures are not particularly applicable to lesions of the rectosigmoid or higher, or to those higher than perhaps 12 cm. above the dentate line, because of the length of bowel necessary to permit an adequate resection proximally and the necessity of saving sufficient bowel to extend beyond the anus. Lesions at this level or higher can usually be treated more satisfactorily by segmental resection with primary anastomosis.

While pathologic findings strongly supported the concept that carcinoma of the mid and upper parts of the rectum could be treated as adequately by pull-through procedures as by combined abdominoperineal resection, it remained to be demonstrated whether late survival rates after the two types of procedures would prove the same. It can now be stated with some confidence that this is so, at least after sphincter-saving procedures specifically. Bacon reported that 157 of 300 patients (52.3%) were living five or more years after operation, while Waugh and co-workers [13] found that 61 of 115 patients (53.0%) were living after this interval. The survival rates in the two series are not only identical but also entirely in keeping with those reported after treatment of lesions at the same level in the bowel by combined abdominoperineal resection.[5,9]

It probably cannot be concluded with complete confidence as yet whether the results after endorectal resection will be equally good. However, on the basis of a relatively small number of cases it would appear that late survival rates will be similar. All 30 patients in the present series who survived nonpalliative resections for frank carcinoma carried out prior to 1952 have been followed to the present. Sixteen (53%) are living and presumably well five or more years after resection.

Summary

Combined abdominoendorectal resection is a pull-through procedure in which a colonic stoma opening into the most distal 3 to 4 cm. of rectum is achieved. The procedure has been carried out in 114 cases. The risk is comparable to that of combined abdominoperineal resection. Serious complications included extensive sloughing of the colon (4 cases), pelvic abscess in the absence of sloughing (10 cases), and failure of union between the colon and the rectum (2 cases). Three permanent and two temporary abdominal colonic stomas were necessitated as a result of sloughing or infection. It is probable that the incidence of complications can be reduced materially.

Fecal control after endorectal resection, in our opinion, is far better than that achieved by sphincter-saving procedures. In the present series, 93 of 101 patients regained essentially normal control, while 8 remained incontinent. The reason for the incontinence was usually evident. Late survival after sphincter-saving procedures and, in all probability, after endorectal resection for carcinoma of the mid and upper parts of the rectum is the same as that after combined abdominoperineal resection.

Experience with endorectal resection is now sufficiently extensive to indicate that it is an entirely feasible procedure for the treatment of carcinoma of the mid and upper parts of the rectum.

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DISCUSSION

ON PAPERS BY DRS. PERZIK, JOERGENSON, CARTER, AND DEEB; DRS. LEHMANN, MORRISON, RUTNER, KOUCKY, AND WILSON, AND DRS. BLACK AND BOTHAM.

DR. DOUGLAS W. MACOMBER, Denver: We are indebted to Dr. Perzik and his co-workers for a tremendous amount of research and for bailing out a bad statistical rate in the substandard group of patients. The five-year over-all salvage rate of intraoral cancer is probably less than 30%. Figures range from as low as 5% to as high as 40%. Neither we nor the radiotherapists can be proud of these statistics. We are both here to stay, and our cooperation is mandatory.

Surgery and irradiation of the primary tumor should be complementary, not competitive. The neck belongs to the surgeons. Cancers located where the tissues are soft yield better to irradiation than those that are over bone or cartilage, where osteonecrosis or chronic ulceration or both may follow. Preoperative irradiation of the primary tumor four to six weeks before surgery may result in its shrinkage and devitalization. Then an operation of glossectomy, hemimandibulectomy, or removal of the inner periosteum and cortex of the mandible combined with neck dissection en bloc may be preferred. Certainly, we can detect a negative implication when our friends refer to this as the "commando" or the "pull-off," rather than the "pull-through," operation.

This plan of procedure, more frequently invoked, should increase our five-year survival rate. Results of irradiation are in direct proportion to the quality, experience, and equipment of the radiotherapist. We must beware of those whose minds are closed to surgery and surgeons, and we shall do well to cooperate with those who know well their limitations and our capabilities.

The question of when to perform neck dissection or to do the combined operation is controversial. Some say: "Dissect the neck in all cases of cancer of the tongue." Others say: "Do so only if there are palpable nodes." Since metastasis may be in the neck, though not demonstrable, it is reasonable to suppose that the patient's best chance of survival is with early radical neck dissection.

Obviously, whether to dissect or not to dissect entails a calculated risk. Given a tumor of Grade 3 or Grade 4, of rapid growth, over 2 cm. in size, invasive, and in a younger patient, there is no doubt that such a dissection is indicated. But given a patient with a Grade 1 or Grade 2 tumor, of slow-growth, under 2 cm., without metastasis, especially in an older patient, the majority of us would probably be satisfied to excise or irradiate the primary tumor and follow this by periodic observation. Between these extremes will be cases in which the chance of survival depends upon our judgment and early decisive action.

DR. ROBERT S. SMITH, Boise, Idaho: I hope it may not be considered redundant to comment on the fact that some pitfalls still remain in making a firm clinical diagnosis of cancer of the stomach. A recent case emphasizes this point

The patient, a woman 41 years of age, gave a history of poor general health, a gradual loss of 100 lb. in weight during a 10-month period, and progressive anemia. When an acute episode of upper abdominal pain and vomiting brought her to the hospital, x-ray studies demonstrated a large filling defect in the distal half of the stomach. This was interpreted by the roentgenologists as representing an ulcerated neoplasm, in all probability a carcinoma.

At surgery a large ulcer of the greater curvature of the stomach was obvious. This lesion extended deeply into the transverse mesocolon, and its malignant nature was not questioned. A block resection of the stomach and transverse colon, with their related mesenteries, was therefore carried out. A stone-packed gallbladder was removed incidentally.

After surgery, no evidence of malignant disease whatsoever was found in the resected stomach. The patient made an uncomplicated recovery and left the hospital on the ninth postoperative day.

[Slides] The operative specimens in this case are shown. The arrows point to a massive infiltrate extending from the greater curvature of the stomach into the transverse mesocolon.

[Slide] The stomach, opened, shows a typical benign ulcer of large size, actually presenting a mucosal defect 7×3.5 cm. and several centimeters deep, with a smooth base and sharp edges. A similar, but smaller, ulcer is present in a prepyloric position.

DR. FREDERIC W. TAYLOR, Indianapolis: I stand pretty much in awe of what Dr. Lehmann and colleagues have given in the way of figures, for we cannot reproduce them. We wish we could, and we have searched our records to find our mistakes. We think we operate with reasonable care, and we operate in the same manner as others.

Because of our shortcomings, recently Dr. Dempsey Strange and I reviewed surgical cases of gastric carcinoma at the Indianapolis General Hospital, the Indianapolis Veterans' Administration Hospital, and the Indiana University Hospitals. That is a representative group and very similar to Dr. Lehmann's. There were 181 such patients operated upon between 1945 and 1950. We had a 96% follow-up on all these patients, which we thought was good, considering the itinerant type of patients in two of those hospitals. At the end of five years all were dead. There was not one survivor. We have survivors on either side of the five-year period, but we do not have one single survivor in the five-year period—and more than one-third were VA Hospital patients. In our community, therefore, we have a very dim and grim outlook on this disease.

There is one point I should like to bring up, and that is the phrase, "resection or operation for cure," which is encountered in practically every report on cancer of the stomach that has come into the literature in recent years. We are rather confused by that term, for we don't quite understand it.

Does it mean that the surgeon, before operation and after the x-rays and after his complete clinical study of the patient, has said: "I think this patient can be cured"? Does he put that down on the chart? Or is it after the patient has been operated upon and his belly opened, and then does the surgeon write on the patient's chart: "This is an operation for cure"? Or does the surgeon wait until the pathologist sends in his report on the nodes, and so on, and then does he put down on the patient's chart: "This patient was operated on for cure"? Or, does he, as we suspect, wait until a series such as the present one is about to be reported, then go to the record room and, with a stack of charts on the table before him, decide then and there, several years after the operation, that a patient was operated on "for cure"?

DR. CHARLES G. JOHNSTON, Detroit: I listened to Dr. Lehmann's presentation with a great deal of humility. We have not done well, at least in one of our hospitals. Dr. Taylor's discussion makes me feel a bit better, as he indicates he has similar troubles in Indianapolis.

This paper points out that the extent of the disease and the condition of the patient upon whom we are operating have a tremendous amount to do with what we can offer the patient and the results we get.

The Detroit Receiving and the Dearborn Veterans' Hospitals are under the same control; the same residents do the operating, and the same staff members supervise the operation and the care of the patient. The staff surgeons are all qualified and have had similar backgrounds in residency training. In the private hospitals there are more surgeons concerned with variation in technique and concept. There is little difference between the results at the private and at the Veterans' Hospital.

The great discrepancy between the results at the Receiving Hospital and those at the Veterans' Hospital indicates the importance of the type of material concerned. This is obvious not only in relation to carcinoma of the stomach but for other conditions as well. The patients at the Receiving Hospital come to us later and less well nourished than at the Veterans' Administration Hospital.

This points up an important fact—that in any review of a series of cases it is not always the skill of the surgeon that counts; it is what he has to

work with. One might expect great variation in results, depending on the type of cases considered.

I am sure there are other points that will be presented in Dr. Lehmann's published paper which will emphasize some of these things even more strongly than either the authors or I have been able to do.

DR. TOM D. THROCKMORTON, Des Moines, Iowa: I don't come up here because I know anything about carcinoma of the stomach; I come up here to take a poll.

Where I come from, in Des Moines, I have been operating on carcinomas of the stomach for about 15 years. After about the first five years, I began to think that people had found out about me, for I was doing fewer and fewer operations for carcinoma of the stomach. I asked some of the other surgeons in Des Moines, and they got to thinking about it; they discovered that they also were doing fewer operations for carcinoma of the stomach. Then we thought that perhaps the patients were all going to the Mayo Clinic or to Iowa City. I asked my colleagues in Iowa City, and they said the same thing—that, for some unknown reason, they were doing fewer operations for carcinoma of the stomach.

Just out of idle and personal curiosity, I should like a show of hands of those who think there is an absolute decrease in carcinomas of the stomach. Well, evidently it is not just something in the drinking water in Des Moines.

DR. SAMUEL L. PERZIK, Beverly Hills, Calif.: The one thing we learned from our clinical review was that in certain instances elective neck dissection is in order in the management of intraoral carcinoma. There are those who are opposed to the use of elective neck dissection on the basis that therapeutic management will yield equally good results. However, I believe a study of their papers will show that their findings are entirely based upon a philosophical analysis and not upon a review of actually consummated cases. These surgeons do not do elective neck dissections and so, on the basis of statistics and philosophy, rather than on an analysis of actually performed elective neck dissections, they presume that elective neck dissections, under certain conditions, would be of no value.

Even though the cases in our paper were few, the trend did show that if the nodes were positive and were removed by elective procedure, the end-results would be better. Therefore, I believe that, in furtherance of this surgical procedure under these conditions, an elective neck dissection should be performed in cases of carcinoma of the tongue, floor of the mouth, and buccal mucosa, after a unilateral primary lesion is controlled.

DR. GERALD S. WILSON, Detroit: With reference to Dr. Taylor's point—resection "for cure"—we decided the question of whether a patient had resection for cure or for palliation from a review of the operative dictation. This is a backward sort of survey and has all the disadvantages of a backward survey. We hope to continue the study as a forward survey, in which the operating surgeon, at the time of resection, states on the operative chart whether it is for cure or for palliation.

Tumors and Cysts of the Mediastinum

Survey of One Hundred Seventy-Four Mediastinal Tumors Treated Surgically During the Past Eighteen Years at the University of Wisconsin Hospitals

ALFRED J. HERLITZKA, M.D., and JOSEPH W. GALE, M.D., Madison, Wis.

Introduction

A tumor of the mediastinum is no longer considered a medical curiosity. It was once thought to be a lesion of obscurity and inaccessibility, but with the advent of routine and mass-survey chest x-rays and improved surgical techniques it has become a lesion of ready visibility and resectability.

Since many of these lesions are potentially malignant or, by virtue of their size and position, may cause serious symptoms, a review of the salient features of mediastinal tumors in indicated.

This report deals with 174 cases of mediastinal tumors or cysts. It is our belief that this is the largest single series reported from any one hospital.

Methods and Materials

These 174 mediastinal tumors or cysts were operated upon at the University Hospitals from 1939 to 1957. Only lesions which originated primarily from the mediastinum were included in the series. The ages ranged from 2 weeks to 81 years, and the series included 92 female and 82 male patients.

The mediastinum is that space between the pleural sacs which extends from the sternum to the spine and from the thoracic inlet to the diaphragm. Certain arbitrary divisions of the mediastinum are indicated in Table 1. These subdivisions were important in that many lesions had a predilection for certain areas.

Results

There were 174 mediastinal growths operated upon in the 18-year period, and these are classified in Table 1 according to frequency. The neurogenic tumors were most frequent, followed by teratodermoids, bronchogenic cysts, pericardial cysts, thymomas, lymphomas, and intrathoracic goiters.

Figure 1 demonstrates the most frequent location of tumors within the mediastinum, and Figure 2 illustrates the incidence of localization of each major tumor group to a specific subdivision. The neurogenic lesions usually occupied the posterior medi-

From the Department of Surgery, Division of Thoracic Surgery, University of Wisconsin Hospitals.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 21, 1957.

TABLE 1.—*Incidence of Predominant Mediastinal Tumors Compared with that of Other Series*

Type of Tumor	Other Series							This Series	
	1946 (Ref. 1)	1947 (Ref. 2)	1949 (Ref. 3)	1952 (Ref. 4)	1956 (Ref. 5)	Total No.	% of Total	No.	%
Neurogenic	30	6	17	20	58	131	29.1	35	20.1
Teratodermoid	20	4	8	12	16	60	13.3	26	14.9
Bronchogenic cyst	23	5	3	5	21	57	12.7	24	13.8
Pericardial cyst	10	8	2	2	6	28	6.2	17	9.8
Thymoma+cyst	6	3	2	17	20	48	10.7	14	8.0
Lymphatic	10	5	3	11	5	34	7.6	12	7.0
Goiter	2	1	2	5	0	10	2.2	10	5.7
Miscellaneous	8	9	7	29	29	82	18.2	36	20.7
Total	109	41	44	101	155	450	100.0%	174	100.0%

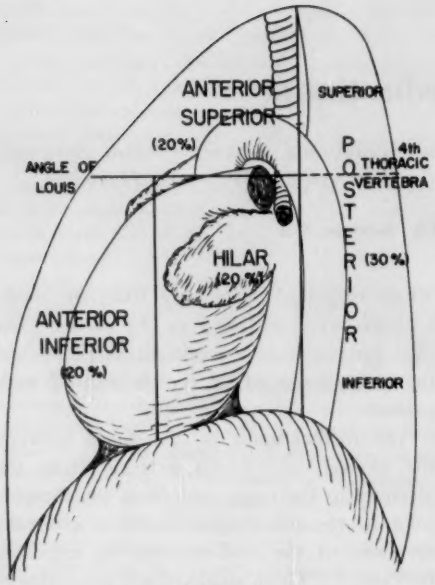


Figure 1

Fig. 1.—Arbitrary divisions of the mediastinum and distribution of 174 tumors or cysts, represented in per cents. Ten per cent were either not well defined or too large to localize.

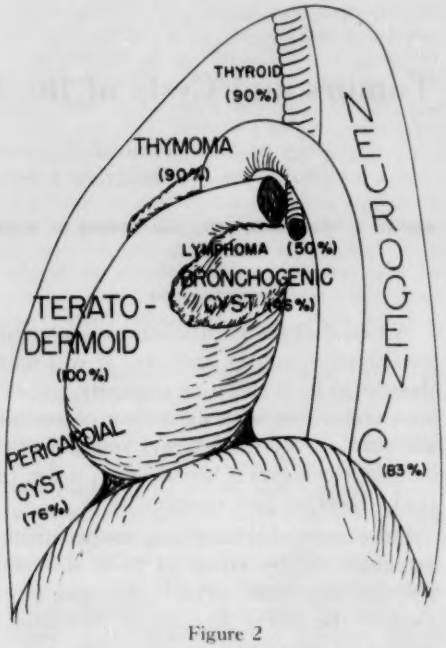


Figure 2

Fig. 2.—Predilection of major tumor groups to certain areas of the mediastinum with the per cent of that specific tumor group occupying the area illustrated.

astinum; the goiters and thymomas were in the anterior superior mediastinum; the teratodermoids and pericardial cysts were in the anterior inferior mediastinum, while the lymphomas and bronchogenic cysts often occurred in the hilar mediastinum.

Of the entire group, 43% were detected either by mass-survey 70-mm. chest x-rays (47) or by routine chest films (28). With the exclusion of the miscellaneous lesions, an accurate radiologic diagnosis was made in 68% of the cases reviewed. Symptoms were nonspecific but present in 62% of the cases. The symptoms encountered most frequently were pain, in 34%; cough, in 30%, and dyspnea, in 21%. Physical examination suggested intrathoracic abnormalities in 9%, rarely being diagnostic and indicating only the presence of a mass or its effect on contiguous structures.

Forty-five tumors, or 25% of the entire series, were malignant. Of the 45 lesions, 20 were resectable, with 10 patients living two or more years without obvious recurrence. Empyema occurred postoperatively in five cases, one patient later requiring a pneumonectomy and another decortication. There were four operative deaths, or a surgical mortality of 2.3%.

Tumors of Neurogenic Origin

The pathologic lesions encountered were as follows:

Benign (77%)	Neurofibroma	19
	Ganglioneuroma	5
	Neurilemmoma	3
Malignant (23%)	Neurofibrosarcoma	3
	Neuroblastoma	3
	Schwannoma	2
	Total	35

Neurogenic tumors were the most frequent lesions found at surgery and comprised 20% of all the mediastinal tumors (Table 1). Among the benign neoplasms the neurofibroma predominated. Of the malignant group, the neuroblastomas occurred most frequently in the younger age

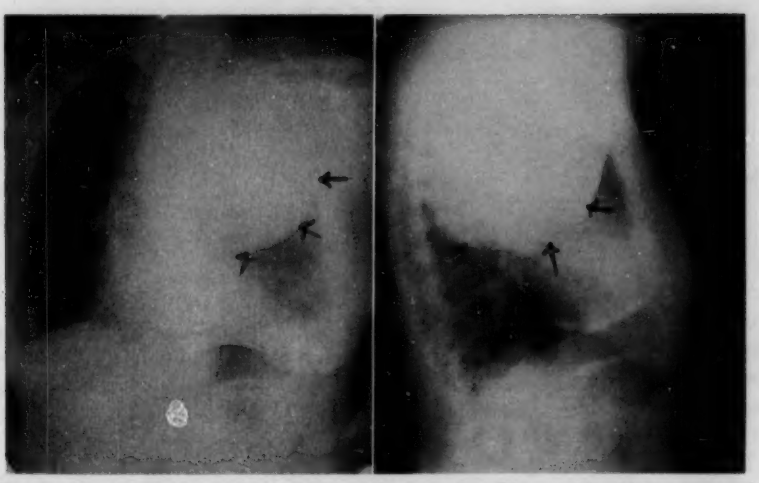


Fig. 3.—Posteroanterior and lateral chest x-rays of a 52-year-old white woman with a one-year history of dyspnea, back pain, nonproductive cough, and unilateral flushing of the face. The large, well-demarcated, homogeneous mass producing tracheal compression and mediastinal shift was a benign neurofibroma.

group, while the neurofibrosarcomas were most prevalent in adults.

As in other series, the posterior mediastinum was the usual location of the neurogenic tumors (83%), especially the neurofibromas (94%). One neurofibroma was observed for 12 years slowly but progressively growing, still being asymptomatic at the time of removal. These lesions varied from 2 cm. to almost complete replacement of the hemithorax (Fig. 3). The patient illustrated had a large neurofibroma, with symptoms of unilateral flushing, dull pain in the back, and a nonproductive cough. There was no Horner syndrome, although with sympathetic chain involvement this syndrome has been manifested.

Pain was the most frequent symptom (40%). The pain was localized at times but often radiated along the distribution of the involved intercostal nerve or to the neck or back.

A patient with Recklinghausen's disease was found to have a neurofibroma at thoracotomy. An "hourglass" extension into the intervertebral foramen, producing weakness of the lower extremities, was noted in two instances, a ganglioneuroma and a neuroblastoma.

Roentgenologically, these tumors appeared rounded, sometimes elongated or lobulated, sharply well-defined, homogeneous shadows. There was rib and vertebral erosion in several cases. At times calcium could be visualized. There was widening of the intervertebral foramen in two patients.

The prognosis was excellent when the lesion was benign. Recurrence of a ganglioneuroma occurred in one patient, but the lesion had been incompletely removed initially because of the precarious condition of the patient at the time of surgery. Of the malignant group, three patients were well two, three, and four years, respectively, after resection of the tumor. The first was a patient with a neurofibrosarcoma who had a craniotomy for a sclerosing tumor of the choroid plexus six months before resection of the mediastinal tumor. The second had resection of a neuroblastoma, followed by x-ray therapy, while the third, with the longest survival, was a patient with an encapsulated neurofibrosarcoma whose chest x-ray was normal two years before the resection.

Teratodermoids

The pathologic lesions encountered were as follows:

Benign	Dermoid cyst	17
	Teratoma	7
Malignant	Teratoma	2
	Total	26

As suggested by Harrington[6] and Blades,[1] the dermoid cysts and teratomas were combined, forming the second most frequent group of mediastinal lesions. The age group varied from 3 months to 69 years, the mean age being younger in the teratoma group (24) as compared with the dermoids (35). There was no sex preference.

One-third of the patients were asymptomatic. The major complaints were cough and pain, which was often substernal or radiating to the shoulder, whereas dyspnea and palpitation occurred less frequently. Three of the patients had a trial of x-ray therapy, without benefit, prior to surgery. This type of lesion tended to grow slowly, so that pressure symptoms usually did not manifest themselves until the second, third, or fourth decade of life.

All these 26 lesions were located in the anterior inferior mediastinum. One lesion extended into the contralateral hemithorax. The combined classification and the characteristic localization could be explained in the supposed common origin from the third brachial cleft, or the same origin as that of the thymus. The lesions were usually discrete, circular, or globular and of homogeneous density. At times calcium, plaques of bone, and teeth were noted. Pleural effusions were present in two of the benign dermoid lesions. One benign teratoma had ruptured into the esophagus, while another had an associated daughter cyst containing hair.

Both the malignant lesions had squamous-cell changes and were nonresectable. One of these was a detectable tumor on a routine chest x-ray 12 years before surgery (Fig. 4).

Bronchogenic Cysts

In this group, of 24 lesions, the tumors were benign, and usually located in the hilar (11) or posterior (7) mediastinum in relation to the trachea and major bronchi.

Fig. 4.—Posteroanterior and lateral chest x-rays of a 69-year-old white man, demonstrating a large, fairly well-demarcated mass with calcification. A routine chest x-ray 12 years before revealed a shadow in the left hemithorax, but there was no follow-up. The patient was asymptomatic until four months before admission. Physical examination revealed left vocal cord paralysis, tracheal deviation to the right, mediastinal widening, clubbing of the fingers, and venous distention, suggestive of obstruction of the superior vena cava. An unresectable malignant teratoma was encountered at surgery.

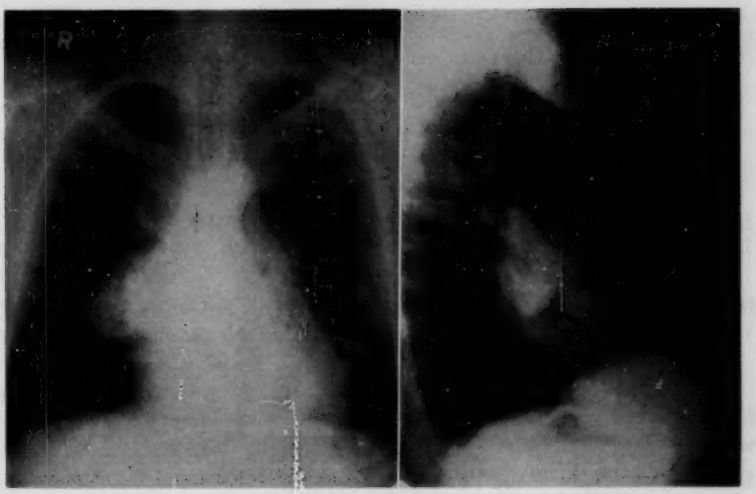


Fig. 5.—Chest x-rays of a 47-year-old white man who had been rejected from military service 13 years before because of a mediastinal shadow. He was asymptomatic until one month before admission, when sharp interscapular pain was noted on the right. Diagnostic studies included serology, chest fluoroscopy, planography, cardiac catheterization, angiocardiography, and bronchoscopy. A vascular lesion was suspected initially, but one sputum specimen was suspected of showing malignant cells. At surgery a bronchogenic cyst was easily removed, but also an unresectable, unassociated bronchogenic carcinoma was encountered.

However, they were found everywhere in the mediastinum.

Usually they were spherical, unilocular, fairly thin-walled cysts, containing mucilaginous material. Typically, the cysts were lined by ciliated pseudostratified squamous epithelium and contained bronchial glands. However, their characteristic mucous lining was destroyed by fluid, pressure, and infection in six cases, thus forming flat or low cuboidal epithelium. The wall often contained smooth muscle, fibrous stroma, and cartilage.

Most of the lesions were detected in the third and fourth decades. There was an even sex distribution, symptoms being mild and primarily respiratory. All the cysts were resected. Only one of the lesions communicated with the tracheobronchial tree, producing an air-fluid level on the roentgenogram; however, the usual appearance was that of a smooth, rounded mass, having the density of fluid.

Figure 5 illustrates a diagnostic case in a 47-year-old white man who had been rejected from military service 13 years before admission because of a mediastinal shadow.

Pericardial Cysts

These unilocular, thin-walled, benign lesions (17 cases) were composed of fibrous connective tissue walls lined by flat or cuboidal endothelial or mesothelial cells. Because of the failure to agree on the pathogenesis, these cysts have been associated with various terms (pericardial celomic cyst, spring-water cyst, serosal cyst, and mesothelial mediastinal cyst [7]).

The lesions were usually asymptomatic (53%) and were typically located in the anterior inferior mediastinum (11). On roentgenogram the cyst usually appeared as a smoothly rounded, sharply demarcated lesion of uniform density, lying against the pericardium, diaphragm, and chest wall. Because of this position, the lesions were occasionally confused with a diaphragmatic hernia, dermoid cyst, or pericardial fat pad. One lesion communicated with the pericardial cavity, forming a rare pericardial diverticum (Fig. 6). All the cysts con-

tained a clear, serous fluid and were readily removed.

Thymomas and Thymic Cysts

The pathologic types encountered were as follows:

Benign (71%)	Simple thymoma	5
	Lymphoendothelioma	3
	Thymic cyst	2
Malignant (29%)	Lymphoendothelioma	3
	Lymphosarcoma	1
	Total	14

The thymomas occurred less frequently in this series than in several other series recently published (Table 1). A possible explanation is the stress which has been placed on the association of thymomas and myasthenia gravis. Up to 15% of myasthenia gravis patients have been reported to have a thymoma.[8] There were two such patients with myasthenia gravis in this series. Both lesions were histologically malignant lymphoendotheliomas. No symptomatic improvement was noted after resection of the lesion. Pleural effusion was present in one benign and one malignant thymoma. All the benign lesions were completely excised except one large, vascular thymoma, which had to be packed to stop bleeding (Fig. 7). During a second procedure, to control the hemorrhage, the patient ultimately died.

Three of the malignant group were resectable. Two patients had pleural implants, but in one patient all the obvious nodules were easily excised. The patient with a lymphosarcoma had skull metastasis one year after surgery. Two patients with malignant lesions were without recurrence two and three years after surgery, respectively.

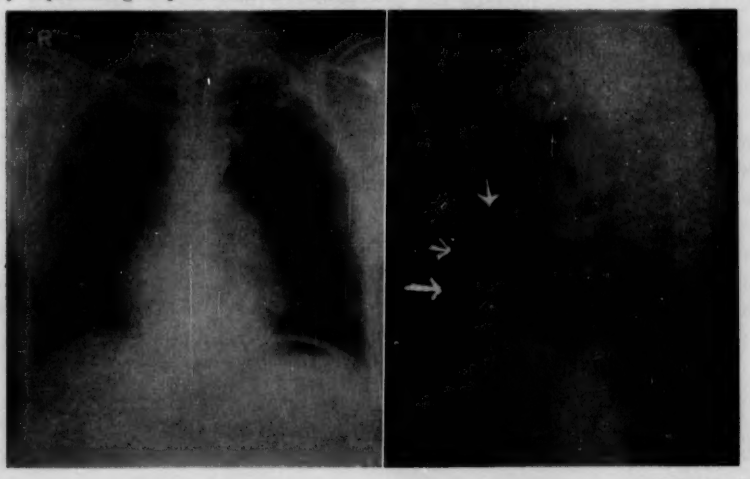
Two of the thymoma patients gave a long history (30 and 9 years) of an intrathoracic abnormality, with significant symptoms occurring only after the lesion had attained considerable size. Most of the thymomas were well demarcated and occasionally had the configuration of a thymus.

Lymphomas

The pathologic types included lymphosarcoma, 7 cases; lymphoblastoma, 2 cases; Hodgkin's disease, 2 cases, and simple lymphoma, 1 case, a total of 12 cases.

The lymphomas are actually the most frequent lesions in the mediastinum, but most of them are diagnosed without a thoracotomy and are treated by x-ray or chemotherapy.

Fig. 6.—Chest x-rays revealing an elongated, well-demarcated, homogeneous mass along the left cardiac border. The contents of the mass communicated with the pericardial cavity, thereby representing a pericardial diverticulum.



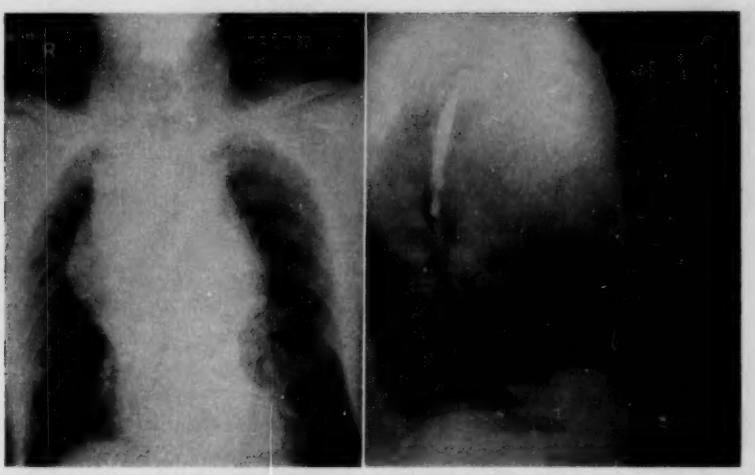


Fig. 7.—Chest films of an 81-year-old white man with a bilateral large globular mass of the anterior superior mediastinum. The patient had gradual onset of dyspnea and dysphagia. The lesion was a benign thymoma.

Most of the lesions in this series occurred in the hilar (six) or anterior (five) mediastinum. The ages varied from 23 to 66 years, with a mean of 51 years, and there was no sex preference. All the patients were symptomatic, with varied symptoms of cough, pain, weight loss, dyspnea, wheezing, and hoarseness. One patient had fever periodically. The differential diagnosis varied greatly before surgery.

Of the group resected, three were well, without obvious recurrence, two, three, and seven years after surgery; one of these patients received x-ray therapy. One patient of this group had an abdominoperineal resection for an unknown neoplasm of the

Fig. 8.—Chest x-rays of a 69-year-old white man who developed symptoms two weeks after a mass-survey 70-mm. chest x-ray had been read as abnormal. In the cervical region the trachea was deviated to the left. The lateral chest x-ray suggested a superimposed nodule at the base of the mass. The impression on fluoroscopy was a malignant tumor of the thyroid. Radioactive I^{131} uptake was increased over the mass posteriorly. Biopsy of a cervical lymph node did not reveal disease. At surgery an unresectable lymphosarcoma was found.

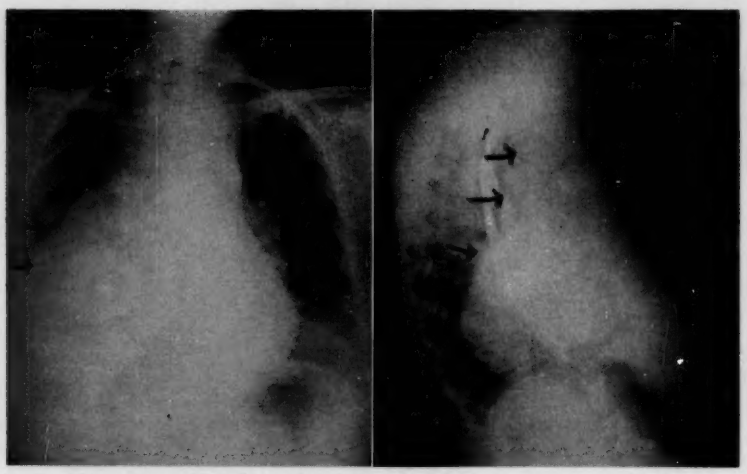


Fig. 9.—Chest x-ray of a 54-year-old white woman with symptoms of hyperthyroidism. The huge mass extending from the supraclavicular region to the diaphragm was a toxic goiter. After removal the symptoms disappeared.

TABLE 2.—*Miscellaneous Tumors of Mediastinum*

No.	Pathologic Diagnosis	Age	Sex	Duration of Symptoms	Location in Mediastinum *	Routine or Mass X-Ray	Comments
1	Carcinoma±thyroid	64	M	2 mo.	P		Biopsy; died 3 mo. p. o.
2	Carcinoma	41	M	2 mo.	P		Excised; encapsulated; died 3 mo. p. o.
3	Carcinoma±lymphoid	56	M	2 mo.	A		Biopsy; died at home
4	Carcinoma±squamous	43	M	12 mo.	A		Excised; well 2 yr. p. o.
5	Carcinoma	64	M	24 mo.	H		Biopsy; esoph. & bronchogram normal
6	Malig. epithelioma±(thymus)	40	M	6 mo.	AS		Excised; well 7 yr. p. o.
7	Cyst, nonspecific	27	F		AI	+	Excised; lining destroyed
8	Cyst, nonspecific	69	F		AI	+	Excised; lining destroyed
9	Cyst, nonspecific	1	M		AI		Excised; epithelial
10	Cyst, nonspecific	42	F	3 mo.	A		Excised; 10×20 cm.
11	Lymphangioma	23	F		AS	+	Excised; multiocular
12	Lymphangioma	24	F	6 mo.	AS		Excised
13	Lymphangioma	34	F		AS	+	Excised
14	Retic-cell sarcoma	39	F	1 mo.	AI		Biopsy; died 16th p. o. day
15	Retic-cell sarcoma	48	M	4 yr.	H		Excised, 5×6 cm.; died 1 yr. p. o., cerebral metastasis.
16	Retic-cell sarcoma	42	M	2 yr.	H		Biopsy; died 2 yr. p. o.
17	Gastroenteric cyst	2 wk.	F	2 wk.	P		Excised; no esoph. communication; gastric mucosa
18	Gastroenteric cyst	13	F		P		Excised; no commun. gastric mucosa
19	Cystic hemangioma	22	F		AS	+	Excised
20	Cystic hemangioma	43	M		AI		Excised with lower lobe
21	Leiomyoma	26	M	18 mo.	P		Excised; had 3 lobes (esophageal)
22	Leiomyoma	34	M		P		Excised; adjacent to esophagus
23	Osteochondroma	26	M	4 mo.	P		Excised; 10×7 cm.
24	Osteochondroma	54	F		P	+	Excised; enlarged in 2 yr.
25	Leiomyosarcoma	27	F	3 yr.	P		Excised; recurred in 2 yr.
26	Lymphoangiosarcoma	3 mo.	F		AS		Biopsy; cyanotic at birth; x-ray Rx; died elsewhere
27	Lipoangiosarcoma	22	M	2 wk.	A		Biopsy; x-ray Rx; died at home
28	Lipoma	35	M		A	+	Excised; size of football
29	Osteoma	48	F		H	+	Excised; pedunculated off pericardium
30	Embryoma	69	M	2 yr.	H		Excised; encapsulated; died 2 yr. p. o.
31	Plasmacytoma	49	F		P		Partial exc.+laminectomy; x-ray Rx; still growing 4 yr. p. o.
32	Fibromyxosarcoma	41	M	1 mo.	P		Excised; recurred; died 1 yr. p. o.
33	Fibromyxoma	34	M	1 mo.	P		Biopsy; x-ray Rx p. o.; no benefit
34	Fibrosarcoma	18	M	1 yr.	P		Excised; died 1 yr. p. o.; pulmon. metas.
35	Fibrochondroma	2	M		AI		Excised
36	Chondromyosarcoma	47	M	3 mo.	P		Biopsy; involved diaphragm

* P indicates posterior mediastinum; A, anterior mediastinum; H, hilar mediastinum; AS, anterior superior mediastinum; and AI, anterior inferior mediastinum.

rectum seven years ago. Three years ago he had a resection of a mediastinal lymphosarcoma and at present shows no recurrence.

Figure 8 illustrates a large, unresectable lymphosarcoma. Because of increased I^{131} uptake over the mass, the lesion was misdiagnosed as an intrathoracic thyroid.

Intrathoracic Goiters

The pathologic types included benign goiter, 9 cases, and malignant goiter, 1 case, a total of 10 cases.

These lesions were characteristically located in the anterior superior mediastinum (nine), with frequent extension inferiorly. Two lesions had retroesophageal extension; three were bilateral, and three had an associated enlarged cervical thyroid. Of the unilateral lesions, six of the seven were located on the right side.

The mean age was 60 years, with six of the lesions occurring in females. Half of all these tumors were detected by routine chest x-ray. Symptoms were present in 40%, consisting primarily of dyspnea, cough, pain, and dysphagia. Two of the patients had toxic thyroid; one died 44 hours after surgery, and the other was markedly improved after resection of a goiter that extended to the level of the diaphragm (Fig. 9). The patient with a papillary adenocarcinoma of the thyroid had a cervical thyroid adenoma palpated 10 years previously. Seven years after resection of the intrathoracic carcinoma, the patient had myxedema and bilateral pulmonary metastasis.

At surgery, a residual, smaller left lobe of the intrathoracic goiter was overlooked on one case and was detected on follow-up chest x-ray. However, the patient died on the sixth postoperative day, of excessive endobronchial secretions, despite several bronchoscopies and a tracheostomy.

Miscellaneous Lesions

A detailed description of these tumors (36) is given in Table 2. Of the lesions in this group, 18 were malignant, and all but 10 of the growths were completely excised. One patient with an unresectable reticulum-cell sarcoma died on the 16th day after surgery. She had received a chemotherapeutic agent, after which treatment pancytopenia, multiple hemorrhages, and fatal infection developed. Only 2 of the 18 patients with malignant lesions were without a recurrence two and seven years after surgery, respectively.

Comment

Lesions within the mediastinum are indeed intriguing to the surgeon and diagnostician. On posteroanterior and lateral chest x-rays, he may predict the nature of the lesions by its location, as shown in Figure 2. However, too often the x-ray is misleading, as the lesion actually occurs elsewhere in the mediastinum. Furthermore, the lesion may be a rare histologic type, making the diagnosis impossible. He must also consider other conditions which may be mistaken for mediastinal growths, such as cardiovascular abnormalities, diaphragmatic defects, or esophageal and pulmonary lesions. Four patients during this period were found to have an aneurysm at surgery, instead of the anticipated mediastinal tumor.

Nearly all the lesions were operated upon through a posterolateral incision. When several of the intrathoracic goiters could not be removed through a routine cervical incision or when a large or bilateral anterior mediastinal growth was encountered, a sternal splitting incision was utilized.

Fortunately, 75% of the mediastinal growths were benign. Removal of these lesions usually gave complete immediate relief of symptoms.

There were 45 malignant lesions, an incidence of 25% of the entire 174 cases. Several of these lesions had been detected years before; so one might postulate that a premalignant lesion could have been removed had operation been performed earlier. Despite malignancy, 20 lesions were resected and 10 of those patients were without obvious recurrence two or more years after surgery.

Benign lesions, though not histologically malignant, may behave as such by virtue of their size and location. These growths cause pressure or infection, or even rupture into vital structures, with resultant serious symptomatology and possible death. Since nearly all these lesions are resectable, as also are many of the malignant ones, once a mediastinal tumor or cyst is detected, surgery should not be delayed.

Summary

During the past 18 years operation was performed on 174 mediastinal tumors or cysts at the University Hospitals.

The operative mortality was 2.3%.

No symptoms were present in 38% of the cases.

Mass-survey or routine chest x-rays resulted in the detection of 43% of the lesions.

Localization of the lesion aided in the preoperative diagnosis.

Malignancy was noted in 45 cases, with 10 lesions apparently without recurrence two or more years after resectional surgery.

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Preoperative Evaluation of Patients with Clinically Resectable Bronchogenic Carcinoma

Role of Biopsy of Nonpalpable Scalene Nodes

THOMAS W. SHIELDS, M.D., and EVERETT SHOCKET, M.D., Chicago

Introduction

The prognosis in a case of bronchogenic carcinoma is distressingly poor for long-term survival. The influence of the cellular type, the extent of local disease, and the presence, or absence, of lymphatic and blood-borne metastases at the time of diagnosis on the ultimate fate of the patient have been well documented. Of course, the biological behavior of the tumor and the host-tumor relationship are undoubtedly of great importance in determining the eventual outcome. Unfortunately, these factors cannot be assessed by any method of investigation at this time. When the disease is confined to the lung, and occasionally to the adjacent mediastinal nodes, the surgical excision of the involved lung and its lymphatic drainage area is accepted as the treatment of choice and is believed to give a better prognosis for long-term survival. However, if the disease has spread beyond the confines of the surgical excision, the removal of the primary growth is of little avail, although occasionally it may be beneficial as a palliative measure. Therefore, one of the aims of the preoperative evaluation of the patient with bronchogenic carcinoma should be directed to exclude the case in which a pulmonary resection would be of no benefit.

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From the Department of Surgery, Northwestern University Medical School, and the Veterans' Administration Research Hospital and Passavant Memorial Hospital.

Recently biopsy of the scalene lymph nodes has been advocated as an additional step in an attempt to fulfill this aim. The lymphatic drainage of the lungs and mediastinum is such that the deep supraclavicular lymph nodes (scalene nodes) may become involved by the disease process arising in the thorax. When the nodes are palpable, there is no question that an excisional biopsy is indicated. However, when nodes are not palpable, the question arises as to the value of routine biopsy in a case of clinically resectable carcinoma of the lung. To formulate an answer to this question, the records of 97 patients who have had a biopsy of nonpalpable scalene nodes have been reviewed. These procedures were carried out on the thoracic surgical service of the Veterans' Administration Research Hospital and Passavant Memorial Hospital. Of the 97 records reviewed, 47 were found to be suitable for inclusion in the present study.

Selection of Cases

The cases selected for this study were required to fulfill two criteria. The first was that the diagnosis of carcinoma of the lung be confirmed histologically either before or after thoracic exploration. The second was that the lesion be regarded as clinically resectable. Contraindications to clinical resectability were (1) lymphatic metastases beyond the confines of the ipsilateral hemithorax; (2) blood-borne metastases to the central nervous system, skeleton, or other viscera; (3) pleural effusion, when tumor cells or blood was demonstrated or when there was rapid recurrence; (4) paralysis

of the contiguous recurrent nerve, the cervical sympathetic chain, or the brachial plexus; (5) superior vena cava obstruction, and (6) involvement of the trachea or carina by the lesion, as visualized by bronchoscopy. Neither paralysis of the phrenic nerve nor direct extension involving the chest wall was considered an absolute contraindication. However, only one patient with chest wall involvement demonstrated preoperatively was included, and this patient successfully underwent pneumonectomy with en bloc removal of the involved chest wall. No patient with phrenic nerve paralysis alone occurred in this group.

Scalene node biopsies were done on the 47 patients between May, 1954, and September, 1957. Seven biopsies were done before January, 1956. The remaining 40 were done in the 21 months preceding this report as a routine preoperative procedure.

Technique and Selection of the Side of Biopsy

The technique utilized in the biopsy of the nonpalpable scalene nodes was essentially as described by Daniels,[1] with some minor modifications. The biopsy is performed under local anesthesia. The incision is usually 4 to 5 cm. in length and is centered over the lateral head of the sternocleidomastoid muscle, 1 to 2 cm. above and parallel to the clavicle (Fig. 1*A*). Generally the lateral head of the above-mentioned muscle is divided (Fig. 1*B*), giving excellent exposure to the fatty tissue in the triangle bounded by the omohyoid muscle, the internal jugular vein, and the subclavian vein, and lying on the anterior scalene muscle. The deep enveloping layer of cervical fascia is divided, and the fat pad and contained nodes bounded by the triangle are readily removed (Fig. 1*C*). In addition, it is important that the fibrofatty tissue which lies under the jugular vein medial to the anterior scalene muscle be likewise removed (Fig. 1*D*). The wound is then closed in the standard manner with nonabsorbable sutures of fine silk. Drainage by means of a small piece of rubber dam is frequently used.

The side selected for the biopsy has been governed by the location of the primary lesion and the lymphatic drainage pathways of the lung (Fig. 2), as described by Rouvière.[2] The right side has been selected

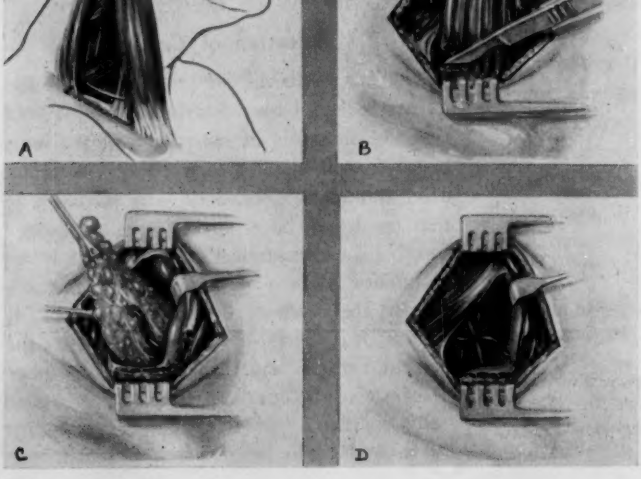

Fig. 1.—Scalene node biopsy: *A*, location of incision and related structures; *B*, division of lateral head of sternocleidomastoid muscle; *C*, removal of scalene fat pad and contained nodes; *D*, surgical field after removal of fat pad and fibrofatty tissue medial to anterior scalene muscle.

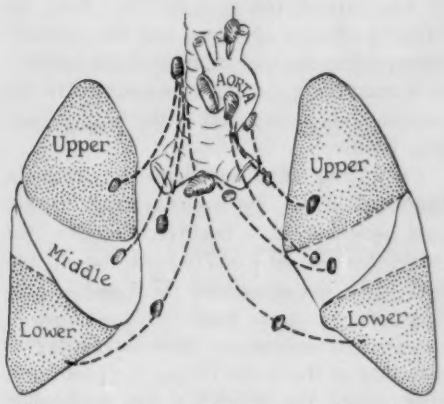

Fig. 2.—Lymphatic drainage of the lungs (Rouvière, H.: Anatomy of the Human Lymphatic System, translated by M. J. Tobias, 1938, redrawn by permission of the publishers, Edwards Brothers, Inc., Ann Arbor, Mich.).

when the lesion is on the right; the left side, when the tumor is in the upper third of the left lung, and bilateral biopsy, when the lesion is elsewhere in the left lung.

Results

In the series of patients with clinically resectable carcinoma of the lung, 47 had excision of nonpalpable scalene nodes. All were men; 38 were Caucasians, and 9 were Negroes. The youngest patient was 38, and the oldest was 73. The average age was 58.7 years.

Of the 47 biopsies, 32 were done on the right, 13 were done on the left, and 2 were done bilaterally. It should be noted that, despite the plan of bilateral biopsy for left lower lobe lesions, only two were carried out in the six patients with such lesions. Two had biopsy on the right only and two on the left side. Lymph nodes were present in all specimens, and the number varied from 2 to 12, the average being approximately 5 nodes per specimen. Histologic examination revealed metastatic tumor to be present in the nodes of three patients of the group. Two of these biopsies were on the right side; the other on the left. Thus, the biopsy of nonpalpable scalene nodes revealed the presence of metastatic disease in 6.3% (Table). It is of interest to note that in three additional patients the histologic examination of the nodes was interpreted as showing chronic granulomatous inflammation compatible with tuberculosis. Of these three, one had previously been treated for tuberculosis; one had active tuberculosis at the time, and in the third a similar histologic finding was made in the subcarinal nodes removed at surgery, but positive culture for acid-fast organisms was not obtained.

To evaluate these results, the x-ray findings, the primary site of the lesion, the histologic cell types, the positive yield of other diagnostic procedures, and the surgical therapy employed in the 47 cases were reviewed.

Roentgenographic Findings.—In reviewing the chest roentgenograms of these patients, it became apparent that they could best be separated arbitrarily into three categories. Group A consisted of six patients in whom the finding was that of a predominant hilar mass with or without infiltration into the pulmonary parenchyma. Group B was made up of 23 patients in whom the finding was that of bronchial obstruction with or without secondary infection, the lesion being main stem, lobar, or segmental in location. Group C was composed of 18 patients with peripheral pulmonary lesions. All three positive scalene node biopsies were obtained in Group A, i. e., those with a predominant hilar mass.

Scalene Node Biopsy Findings in Patients Thought to Have Clinically Resectable Carcinoma of the Lung

Side of Biopsy	
Right	32
Left	13
Bilateral	2
Metastatic tumor present	3 (6.3%)

Site of Lesion.—The location of the carcinoma was determined by bronchoscopy, x-ray, and examination of the lung. Thirty of the carcinomas arose in the right lung. Of these, 13 were in the upper lobe, 2 were in the middle lobe, 13 were in the lower lobe, and the remaining 2 could not be localized other than that they arose from the right hilar area. Seventeen of the car-

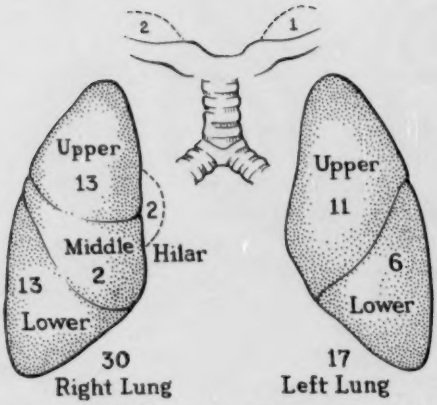

Fig. 3.—Distribution of carcinoma of the lung in 47 patients thought to have clinically resectable lesions. The biopsy of nonpalpable scalene nodes revealed metastatic disease in two on the right and in one on the left.

cinomas arose from the left lung; eleven took origin in the upper lobe, and six, in the lower lobe (Fig. 3). The two positive right scalene node biopsies were in the two patients with the tumor that could only be localized to the right lung in the hilar area. The positive left scalene node biopsy was in a patient with a lesion in the lower-lobe bronchus but with an associated prominent hilar mass and infiltration into the left upper lobe.

Cellular Type.—The cellular pattern of the tumors has been classified into four types. There were 16 moderately or well-differentiated epidermoid and 14 poorly differentiated epidermoid carcinomas. Fourteen were classified as undifferentiated-cell carcinomas. The remaining three were adenocarcinomas. Two of the positive scalene node biopsies were in the undifferentiated group, and the third was in a patient with a poorly differentiated epidermoid carcinoma.

Diagnostic Procedures.—Of the 47 patients studied, bronchoscopy was done in 42. The bronchoscopic biopsy was positive in 46.8% of the entire group. The cytologic smear of bronchoscopic aspiration material was positive for or highly suggestive of tumor cells in 25 patients. The positive diagnostic finding in 40 patients in whom it was carried out was 62.5%. Both the bronchial biopsy specimen and the cytologic smear were positive in two of the patients with metastatic disease demonstrated in the scalene node biopsy, and in the third neither was positive.

Combining all three diagnostic methods, bronchial biopsy, cytologic smear, and scalene node biopsy, a positive diagnosis was established in 30 (63.7%) of the 47 patients. In the remaining 17 (36.3%) the diagnosis was made from tissue obtained at the time of operation. It is interesting to note that of the x-ray Group A (prominent hilar mass) the diagnosis was established by one of the diagnostic methods in all cases. In the x-ray Group B (bronchial obstruction), the diagnosis was made preoperatively in all but two cases. In Group C (peripheral lesions), in only 3 of the 18 patients was the diagnosis established prior to surgery, and in each instance it was by a positive cytologic smear.

Therapy.—Of the 47 patients who were originally thought clinically to have resectable lesions, metastatic carcinoma was found on the scalene node biopsy in 3, and no surgical therapy was offered to these patients. Surgery was not offered to four additional patients, owing to extremely poor pulmonary function in two, an acute coronary infarction in one, and heart failure with an associated old cerebral vascular accident in the fourth. Three patients refused surgical intervention. All 10 patients received x-ray therapy.

Thirty-seven patients were explored surgically. In 13 patients (35.1%) the lesion was deemed nonresectable, owing to advanced local spread or extensive mediastinal node involvement. Twenty-four patients (64.9%) had a resection performed. The type of resection was dependent on the extent of the disease and the general condition of the patient. Fourteen pneumonectomies, nine lobectomies, and one wedge resection were carried out (Fig. 4).

In the group with resection, mediastinal, hilar, or peribronchial lymph node involvement was found in 10.

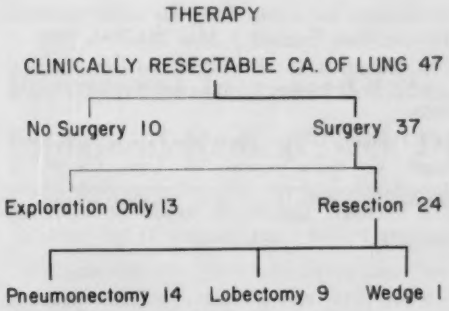

Fig. 4.—Diagrammatic presentation of the surgical therapy employed in the 47 patients.

Comment

In our series of 47 patients with carcinoma of the lung thought to be clinically resectable, biopsy of nonpalpable scalene nodes revealed the presence of metastatic carcinoma in 3. This gave a positive yield of 6.3%. This figure is in accord with the report of Schwippert and Macmanus,[3] who obtained 6 (8.5%) positive scalene node biopsies in 71 cases of histologically proved carcinoma of the lung. The finding of Seghers et al.,[4] who reported a 10.6% incidence of metastatic involvement in a series of 132 patients with known carcinoma of the lung, is essentially similar. It is of note that neither of these authors used as rigid a criterion of case selection as in the present report. In contrast to these series is that of Harken et al.,[5] who obtained a positive biopsy rate of 39.8% in 78 cases. However, in this group tissue was removed from the superior mediastinum, as well as from the scalene area. In no instance was this performed in the present series. It has been our experience that positive paratracheal nodes per se do not render the lesion nonresectable. In several cases such nodes have been removed in performing a pneumonectomy with mediastinal dissection, though admittedly such metastatic involvement carries a poor prognosis for the patient. Connar[6] reported an incidence of 31% positive biopsies, and Umiker and co-workers[7] obtained a 24% positive yield. However, the case selection and other factors make it difficult to compare results.

The three positive scalene node biopsies were obtained in patients with a prominent hilar mass in the roentgenograms of the chest; none were discovered in those with bronchial obstruction or with a peripheral lesion. This is in contrast to the findings of Umiker et al.,[7] who discovered a high degree of involvement with peripheral lesions. This was undoubtedly the result of a high proportion of adenocarcinomas in that series, which tend to metastasize to the cervical area readily. In the present series only 3 of the 18 peripheral lesions were adenocarcinomas.

As reported in other series, undifferentiated-cell carcinoma was found most commonly to metastasize to the scalene nodes. No comment may be made as to the location of the primary lesion; our belief is that the roentgenographic finding of "hilar" involvement is of more importance than location per se.

Summary and Conclusions

The biopsy on nonpalpable scalene nodes in 47 patients with clinically resectable carcinoma of the lung disclosed metastatic disease in 3 (6.3%).

It is concluded that the procedure does not have a sufficiently high positive yield to justify its routine use in all clinically resectable cases of carcinoma of the lung.

Its employment preoperatively is advised in those cases with a prominent "hilar mass" on the chest roentgenogram, or when the bronchoscopic biopsy tissue or cytologic smear reveals the presence of an undifferentiated-cell carcinoma.

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Permanent Increased Intracranial Pressure Following Unilateral Radical Neck Dissection

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Because of the intimate association of the deep cervical lymph nodes with the internal jugular vein, this structure is usually sacrificed in a radical neck dissection. The writings of earlier authorities reflect hesitancy in doing this for fear of the resultant disturbances in circulation of the brain. It has become apparent, however, that such fears were largely without foundation, and the removal of one internal jugular vein, together with all of its tributaries, is now an inherent part of the operation.

Cerebral disturbances following removal of the jugular vein have been reported by some authors[1,2,5-7,9] and denied by others.[8,13] All agree that the chances of increased intracranial pressure are much greater when both internal jugular systems are ablated than when a single side is removed. Furthermore, the longer the interval of time between the removal of the two sides the less chance there appears to be of such complications, the greatest difficulties being encountered when simultaneous removal is practiced. Serial tabulations of spinal fluid pressures made in the immediate few days following the operation show the increased intracranial pressure to level off toward normal values as collateral pathways come into play (Fig. 1). The ability of the patient to compensate in most cases for removal of both internal jugular vein systems is shown by Martin's report of 66 patients who received a bilateral neck dissection without a single mortality or serious morbidity.[13]

The purpose of this paper is to report two cases in which permanent increased intracranial pressure developed immediately after simple unilateral radical neck dissection, in which only one jugular vein and its

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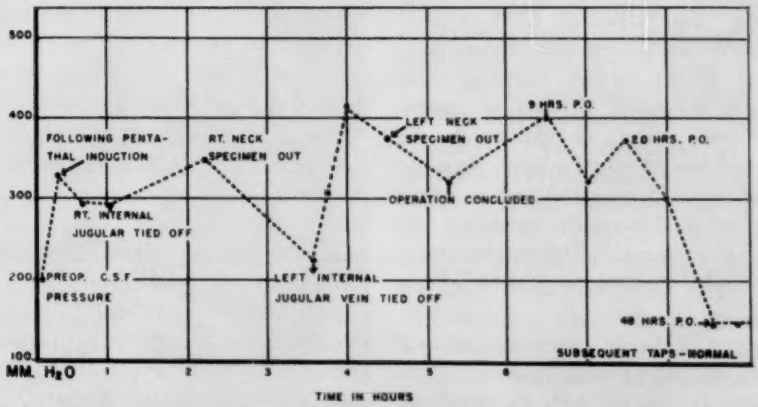


Fig. 1.—Simultaneous bilateral radical neck dissection and concomitant changes in cerebrospinal fluid pressure.

tributaries were removed. The severity of these changes was sufficient to threaten extremely serious consequences, the most important of which was total blindness. In one of the cases the increase in pressure was sufficient to produce a bilateral sixth nerve palsy, in addition to the visual loss. In each case, relief by a subtemporal decompression was obtained, and a satisfactory, but not complete, recovery has been achieved. In a personal experience of over 500 radical neck dissections and experience on the Head and Neck Service of Memorial Center for Cancer and Allied Diseases, New York, involving several thousand neck dissections, and in a survey of the literature, no similar complication was encountered. A discussion of the etiology of this phenomenon and the measures required to deal with it will be presented.

The two patients whose case histories are herein presented were normal persons, unrestricted by any physical handicap prior to the onset of their illness. A simple radical neck dissection for cancer was carried out on the right side in one patient and on the left side in the other. They recovered from the anesthetic and were fully ambulatory within 24 hours after operation. They complained of some headache, but this was not too severe, nor did nausea or projectile vomiting develop. In each case the first thing which aroused the suspicion that all was not well was a complaint of difficulty in reading. This appeared 12 days postoperatively in one patient and 15 days postoperatively in the second. Bilateral sixth nerve palsy developed 15 days postoperatively in one patient, in addition to the diplopia and loss of visual acuity. No other peripheral nerve palsy developed in either case. Spinal fluid pressure exceeding 600 mm. H_2O was recorded. Ophthalmic examination revealed papilledema of 3 to 5 D. in both.

Because of a fairly extensive personal experience in radical neck dissections, together with familiarity with the work of others with more extensive experience, in which we failed to encounter any similar difficulty, we at first refused to consider the possibility that removal of the jugular vein could produce these complications. Inasmuch as both patients had been operated upon for cancer, our first thought was that a metastasis to the brain must exist and be responsible for such findings. The possibility of meningitis was ruled out by the afebrile course. Another possibility was that the patient might have a coexistent second tumor primarily arising in the brain itself and not necessarily associated with the recognized cancer.

In any event, no improvement in the papilledema was noted, and within a few days the visual disturbances had increased so markedly as to make it impossible to read fine print at all, even with glasses or other aids. Consultations with an ophthalmologist resulted in the statement that if such changes persisted, irreversible damage would occur and that in the event that the papilledema should increase beyond present limits, total blindness might develop. It had been our feeling up to this point that the patients would compensate if given a little more time and that nothing further need be done. In the face of such alarming statements by our ophthalmologist colleagues, however, we were afraid to defer any action and, accordingly, called in a neurosurgeon, who performed a subtemporal decompression in both cases. Prior to decompression, a spinal fluid pressure in excess of 600 mm. H_2O was present, and this persisted until the decompression was performed.

We still felt it highly likely that, as the months rolled by, other symptoms would develop to support the concept of an intracranial metastasis or independent brain tumor. After the subtemporal decompression, the papilledema and sixth nerve palsy gradually cleared and the recovery of eyesight approached normal limits. Five years has now elapsed since the first patient was operated upon, and eight months in the second. No recurrence of tumor has developed in either

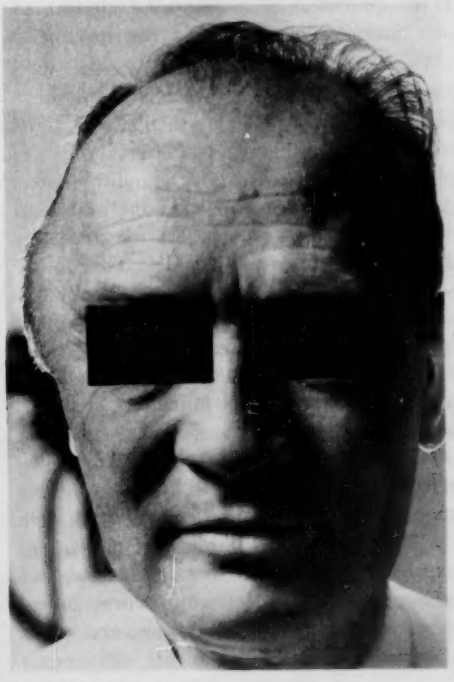
patient, nor has the suspicion of intracranial tumor been substantiated.

In most patients receiving a subtemporal decompression, the temporal bulge will gradually become less noticeable as the increased pressure subsides, and eventually, instead of a bulge, it actually appears as a sunken or depressed defect, particularly while the patient is in the upright position. In neither of these cases has this occurred (Fig. 2), indicating that whatever the factors, vascular or otherwise, that appeared after the neck dissection, they are still at work and that a permanent change was produced, for which (in the absence of the decompressions) the system is still unable to compensate.

Etiology

At the time of any surgical operation, there are many factors at work that will produce a transient rise in intracranial pressure. Such things as anesthesia, coughing coincident with the introduction of an endotracheal tube, straining by the patient while in the light plane of anesthesia, changes in the position of the head, and anoxia, are all known to produce such transitory rises. But the cerebrospinal fluid level quickly returns to normal limits following withdrawal of such stimuli. When an increase in intracranial pressure, as reflected in elevated spinal fluid levels, persists, even when the patient has recovered from the operation, other explanations must be sought.

Fig. 2.—Temporal bulge, persisting five years following subtemporal decompression. Patient had developed signs of increased intracranial pressure following unilateral radical neck dissection, requiring decompression to prevent optic atrophy.



Neurosurgeons recognize that a false-positive Queckenstedt test can occur in the absence of any organic block. Foley,[14] in surveying this problem, states:

> The existence of a condition in which increased intracranial pressure occurs in the absence of a space-occupying lesion or of internal hydrocephalus was first recognized by Quincke (1893, 1897). . . . [The syndrome consists of] prolonged intracranial hypertension without ventricular abnormalities, focal neurological signs or disturbance of awareness or intellect, the most frequent symptoms being headache of moderate degree, obscurations of vision, diplopia and sometimes tinnitus; marked papilloedema and abducens palsies are the only signs.

From his personal experience and a survey of the literature, Foley collected 105 such cases. Forty-six of these had a history of infection in the mastoid or nasal sinuses, and he concurred in the belief that the main etiologic factor in such cases of "otitic hydrocephalus" was thrombosis of the adjacent lateral sinus. There remained 60 cases in which no such history of associated infection was present and in which he referred to the condition as "benign intracranial hypertension." No satisfactory explanation was advanced for these cases, but it is to be recalled that in none of them had any preexistent trauma or operation on the neck taken place, and, so far as could be ascertained, the syndrome appeared "out of the blue."

In our two cases, the appearance of such signs and symptoms so closely followed the operation of unilateral radical neck dissec-

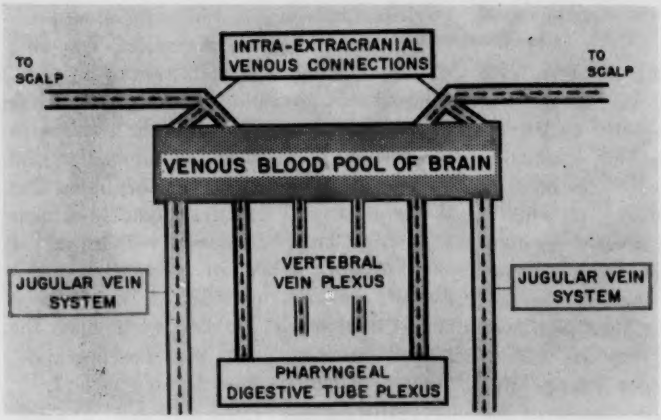


Fig. 3.—Schematic representation of major pathways of blood return from the brain. Potential pathways of venous return from the brain are many and varied but may conveniently be grouped under four headings.

tion that a direct cause-and-effect relationship seems hard to deny. A prime suspect in this regard is the alteration in the return blood flow from the brain following removal of the internal jugular vein with its tributaries. Martin [13] found, when reviewing the standard textbooks of anatomy in an effort to enumerate the potential pathways of blood return from the brain, that "the notes soon became so voluminous as to preclude an attempt to set down all the details in a report." However, study of these return pathways indicate that they may be divided into four major groupings (Fig. 3): (1) internal jugular vein system, (2) vertebral vein system, (3) "pharyngeal-digestive tube" plexus—those veins running down through the nasopharyngopharyngeal wall, pterygoid fossa, etc., and (4) intra-extracranial connections. These last connections traverse the skull and connect with the superficial veins of the scalp, finding their way through the cutaneous pathways to the general circulation. It is clear, therefore, that when one major pathway of return has been obliterated, there exist others which are capable, in most instances, of taking over collateral circulation.

Woodhall [11] has made a study of the venous variations of the brain, using 100 postmortem dural preparations. Careful measurements of the cross-sectional diameter of the major venous pathways were used as an indication for evaluating their flow capacities. He summarized his findings as follows: (*a*) In terms of cross-sectional diameter, there was a predominance of right-sided venous return in 39% and predominance of left-sided return in 13%; (*b*) major disproportion between the two lateral venous sinuses exists in 24%; (*c*) inadequate cross circulation between the two halves of the brain at the region of the torcular Herophili is present in 10% to 15%; (*d*) there is a congenital absence of one lateral sinus in 4% of the specimens.

In the event that neck dissection with removal of a jugular vein is done on a patient in whom the opposite lateral sinus is congenitally absent, the effect is to deprive the patient of two of the major venous pathways of return flow from the brain and may create such a deficit that the patient is unable to compensate for it. The ability of patients to compensate by collateral pathways for the obliteration of a major vascular channel varies extremely. If, for example, the femoral artery is ligated in 10 patients at the level of Poupart's ligament, one might show demarcation at the level of his toes, another at the level of the ankle, and a third at the midleg, whereas others might show demarcation at the midthigh. Such variations in the ability of patients to compensate for vascular deficiencies, we believe, also explain the differences in response to interruption of the common carotid artery, wherein most patients will recover

without difficulty but others may develop hemiplegia, or temporary paralysis, or never awaken from the anesthesia at all.

Though such an hypothesis is supported by the immediate development of increased intracranial pressure following ablation of one internal jugular system in our two patients, and by the morphologic studies of Woodhall [11] and Edwards,[10] it must be admitted that there may exist other, unknown mechanisms which are at play, since the development of a similar syndrome has been reported by Foley [14] in the absence of any such antecedent operation.

Summary and Conclusions

The operation of radical neck dissection which involves sacrifice of the internal jugular vein system, usually on one side, is the most effective way of dealing with metastatic cervical cancer. It is being performed in this country and abroad with increasing frequency, a low mortality rate, and a morbidity well within acceptable bounds. No case of permanent increased intracranial pressure resulting from unilateral sacrifice of this portion of the return blood flow from the brain has ever been published. A transient rise in intracranial pressure has been noted by many observers, but the patients have always compensated as soon as an opportunity for the collateral pathways to come into play has been afforded.

Two cases are herein reported in which an increase in the intracranial pressure following ablation of a single internal jugular vein system developed to a degree sufficient to threaten total blindness. The initial suspicion that such intracranial complications did not stem from disturbances in the vascular pathways, but probably were due to an unrecognized intracranial metastasis or separate primary tumor arising in the brain itself, has not been borne out by long-term follow-ups on these patients. The evidence for this stems from the fact that both patients have now remained well of their original cancers five years and eight months, respectively, and no additional evidence of an intracranial lesion has developed, despite the fact that the increased intracranial pressure has persisted and is only being compensated for by a subtemporal decompression.

The anatomic basis for such a phenomenon is discussed, and it is our opinion that in certain rare cases, there may exist anomalies and lack of development of specific intracranial venous pathways which make it impossible for such patients to compensate by collateral circulation for the removal of one internal jugular vein system.

Report of Cases

CASE 1.—*Present Illness.*—A. aged 45, a white married man, was first seen on Nov. 14, 1952, with the chief complaint of a mass in the right submaxillary area of two years' duration. The tumor was painless and had slowly increased in size, no previous treatment having been received.

Past History.—Twenty years previously the patient had a splenectomy for what was diagnosed as hemolytic anemia. His convalescence from this was uneventful, and no further blood dyscrasia had developed.

Examination.—Physical examination was entirely within normal limits except for the mass in the right submaxillary triangle. Here, there were several rounded tumor masses, averaging 2-3 cm. in diameter. A search on the skin for evidence of a primary tumor was not fruitful, and intraoral examination for the same purpose contributed nothing.

Impression.—Metastatic carcinoma, primary lesion undetermined.

Procedure.—Aspiration biopsy of the submaxillary mass was carried out and resulted in the diagnosis of lymphosarcoma. A blood count was entirely within normal limits. A chest plate and examination of other node-bearing areas failed to reveal any evidences of lymphosarcoma at other sites. On Nov. 25, a radical right neck dissection was carried out. There was considerable involvement of all nodes in the submental and submaxillary triangles, but those in the mid and lower portions of the neck appeared to be within normal limits.

Pathology Report.—Lymphosarcoma, upper right cervical nodes; remainder of nodes in the neck within normal limits.

Postoperative Course.—The patient was discharged seven days postoperatively. Toward the latter part of his hospital stay he complained of difficulty in reading. In follow-up visits, he continued to complain of inability to read and of

"seeing bright lights dance before my eyes." At about the same time, diplopia appeared, and on Jan. 5, 1953 (six weeks after operation) a consultation with an ophthalmologist was obtained. Bilateral papilledema, measuring 3-4 D., was noted. There was no gross muscular imbalance.

One week later, examination by a neurosurgeon showed the following: gait and posture normal; Romberg sign negative; no ataxia; no tremors; pupils normal; bilateral choked disks with hemorrhage and exudates; extraocular muscles normal; reflexes normal; rigidity negative; abdominal, cremasteric, knee, and ankle jerks and Babinski sign all negative; blood pressure 160/90.

The impression was probable expanding intracranial lesion due to lymphosarcoma invading the meninges.

The patient was advised to have intraventricular air studies but refused this diagnostic step. He returned for weekly check-ups, during which time repeated examinations of the eyegrounds failed to show any improvement and his symptoms of decreasing visual acuity persisted. By this time his increased intracranial pressure had been present for almost 10 weeks, and it was the feeling of both the ophthalmologist and the neurosurgeon that unless something was done to relieve the pressure on the optic nerves, irreversible optic atrophy would take place, and possibly even total blindness. Accordingly, on Feb. 24, 1953, a subtemporal decompression on the right side was carried out. The neurosurgeon's operating notes state: "On opening the dura, cerebrospinal fluid gushed out from the subarachnoid space under great pressure."

Follow-Up.—After the subtemporal decompression was carried out, serial check-ups on the status of the eyegrounds showed gradual improvement, with subjective improvement in the visual capabilities. Despite the belief that this complication represented an intracranial metastasis or a separate tumor of primary brain origin, the patient's subsequent clinical course has not substantiated this theory. He has remained entirely well of his lymphosarcoma and has developed no further signs of an intracranial lesion. That the changes presumably produced by the right radical neck dissection have resulted in a permanent incapability on the part of the patient to compensate is demonstrated by the fact that at this date (five years after operation) the patient still has a marked bulge at the site of the subtemporal decompression (Fig. 2). In the upright position, most persons receiving a subtemporal decompression will not show any bulge at all and in many cases will even demonstrate a depressed area. This patient has no period throughout the 24 hours when he is free of a definite convex bulge in this area.

CASE 2.—*Present Illness.*—A 37-year-old white married woman applied for advice in April, 1957, concerning a lump in the anterior neck. The mass had first appeared five years previously, and there had been a definite increase in size in the preceding two years. In recent weeks, "pressure" on swallowing appeared. No hoarseness, pain, or other symptoms were elicited.

Past History.—Negative.

Examination.—The positive findings in the general physical examination were limited to the neck mass. This was apparently arising from the left lobe of the thyroid. The remainder of the neck was normal. There was no evidence of toxicity.

Impression.—Tumor of thyroid, type undetermined.

Recommendation.—Surgical excision.

Procedure.—On April 16, 1957, the neck was explored, and a mass arising from the left lobe of the thyroid, and fixed to the strap muscles, was seen. Frozen-section examination resulted in a diagnosis of mixed papillary and follicular carcinoma. A total thyroidectomy and left radical neck disssection, with removal of the jugular vein, was carried out. Anesthesia involved thiopental (Pentothal) induction and endotracheal intubation, plus cyclopropane. Operation was three hours in length and was executed without apparent complication.

Postoperative Course.—The patient awakened from the anesthesia and was up the next day.

Fourth Postoperative Day: Eating well. One-half the sutures out. Slight fluid under flap; aspirated. Slight edema, left side of face.

Sixth Postoperative Day: Complaining of headache. Slight edema, left side of face.

Eighth Postoperative Day: Feeling better; less headache.

Ninth Postoperative Day: Periods of depression. Lethargic. Complains of feeling tired. Calcium and phosphorus normal. Pulse normal.

Tenth Postoperative Day: Slight dizziness on standing.

Twelfth Postoperative Day: Dizzy. Complains of blurred vision for first time. No headache or pain. Examination of fundi showed bilateral choked discs. Reflexes hyperactive. Left pupil slightly smaller than right; extraocular muscles normal. Reaction to light and in accommodation.

Fifteenth Postoperative Day: Patient responsive. Vision still blurred. Less dizziness. Left ptosis present. Bilateral external rectus palsy present for first time.

Sixteenth Postoperative Day: Neurosurgical consultation obtained. Spinal lumbar puncture. Pressure 600± mm. H_2O. Gold curve normal.

Eighteenth Postoperative Day: Right subtemporal decompression. Patient withstood procedure well.

First Postoperative Day: Better. Still irritable.

Second Postoperative Day: Papilledema improved. External rectus palsies remain.

Third Postoperative Day: Lumbar puncture repeated. Pressure 360 mm. H_2O; reduced to 170 mm. H_2O. Fluid clear.

Sixth Postoperative Day: Lumbar puncture. Pressure 170 mm. of H_2O. Sutures out. Eyegrounds improved.

Seventh Postoperative Day: Up, walking. Vision better.

Ninth Postoperative Day: Patient discharged home.

Follow-Up.—The bilateral sixth nerve palsy improved gradually, and 10 weeks following the decompression all extraocular muscles were performing normally. There was concurrent visual recovery, but some visual impairment persists, six months after operation, in the left eye. The bulge from the decompression is still present, and, although it is less prominent when the patient is standing or sitting, at no time is the area entirely flat or decompressed. There is no sign of recurrence of her thyroid cancer, and the patient is leading an essentially normal existence.

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DISCUSSION

ON PAPERS BY DRS. HERLITZKA AND GALE, DRS. SHIELDS AND SHOCKET, AND DRS. MORFIT AND CLEVELAND.

DR. EARL SANBORN, Chicago: At the annual meeting of the American Association for Thoracic Surgery in 1922, Samuel Robinson, of Santa Barbara, spoke, in his presidential address, on "The Present and Future in Thoracic Surgery." He discussed, among other subjects, tumors of the lung, pleura, and mediastinum. In regard to the last, he stated: "The surgical removal of mediastinal tumors has not met with any degree of success, nor can it be pretended that any particular progress has occurred in this field."

In 1948, or 26 years later, Dr. Gale's colleague presented before this Association in St. Louis a paper entitled "Mediastinal Tumors." At that time 36 such tumors were reported resected, without a mortality. Today he has reported a series of 174 consecutive cases. To my knowledge this is the largest series of mediastinal tumors reported to date from one hospital center. Much progress, therefore, has been made in the 35 years since Dr. Robinson's presentation.

The subject of primary tumors of the mediastinum has been so well covered by Dr. Gale that I should like to discuss another aspect of neoplasms of the mediastinum. Recently 9248 autopsy protocols at the Presbyterian Hospital in Chicago were examined in regard to secondary tumors of the mediastinum. All neoplasms of the lymphoma group were excluded from the study.

[Slide] There were 337 protocols in which metastases involved the mediastinum. You will note that the most frequent primary neoplasms of both sexes are at the top of the list. Over 40 different malignancies were found to provide such metastases.

[Slide] Utilizing the nomenclature of Rouvière, the involved lymph nodes were found in the following areas or lymphatic chains: [Slide] Only the four commonest neoplasms were thus analyzed. You will note that the tracheobronchial nodes were involved more frequently than any of the others, and they lie deep in the mediastinum. The internal mammary chain was mentioned in only one case. [Slide] Another interesting aspect was that, although the lymph nodes could have been recognized grossly, as at the time of thoracotomy, very few of them [Slide] could have been seen on a routine P. A. thoracic roentgenogram, according to the criteria utilized.

[Slide] As a side light on the study, it was decided that a tabulation of the secondary neoplasms by decades in the period studied (1895-1950) might be interesting. [Slide] As you can see, there were increasingly more cases of secondary neoplasms of the mediastinum. Perhaps in another 35 years we shall be able to prevent or treat secondary tumors of the mediastinum, and elsewhere, as well as Dr. Gale and his associates have treated the primary tumors of the mediastinum, as disclosed in their report today.

Dr. John L. Keeley, Chicago: I am sure we all appreciate the tremendous amount of work that has gone into the care of 17 patients with mediastinal tumors. I understand from Dr. Herlitzka that in the manuscript he refers to another type of tumor, which he did not show in his slides, namely, mediastinal lipoma.

Mediastinal lipomas are comparatively rare. About 50 have been reported up to the present time. I have a few slides on two such cases. Everything that Dr. Herlitzka has said about mediastinal tumors and cysts applies just as well to these two tumors, as far as their space occupying-features and their symptoms are concerned.

[Slide] This is an x-ray study of a young housewife who for some time was thought to have heart disease, owing to cardiomegaly and some so-called muffled heart sounds. However, when we saw her, a lateral view of the chest revealed the findings shown on the right side of the screen.

[Slide] This slide shows the operative findings. Here was a sheath of fat enclosing the pericardium and heart. A little more information may be gained about the distribution of the fat from the insert, shown here. Removal of this entire tumor was a relatively simple process.

[Slide] The total specimen removed (in some areas piecemeal) weighed well over 1600 gm.

[Slide] This slide shows the postoperative result. The patient made a complete recovery. There is no more reason to believe that a lipoma in this area might recur than one in any other part of the body.

[Slide] This slide shows a patient with an abnormality in the cardiophrenic angle which we thought was a pericardial cyst. It proved to be a lipoma, also, as shown in this superimposed specimen.

With the morbidity and mortality from thoracotomy decreasing, and with the excellent results that Dr. Gale and his associates have shown following excision, surgical exploration is certainly in order in all of these abnormalities.

In the 75% of these tumors which are benign, their removal will constitute a cure, whereas in the remaining 25% or so which are malignant certainly appropriate therapy can then be instituted on a sound basis.

Dr. Louis T. Palumbo, Des Moines, Iowa: During the past three years, we have performed scalene lymph node biopsies on 51 patients; the nodes were positive in 18%. Of this total, 38 patients had proved carcinoma of the lung; the nodes were positive in 19% (Table 1).

In three of the seven cases with positive biopsy, the nodes were nonpalpable. In four cases the pulmonary lesion was in the upper lobe, and in the remaining three the mass was in the hilar region (Table 2).

Of the 19 cases in which the carcinoma was considered operable prior to scalene node biopsy, 2 (10%) had positive nodes, whereas of the 19 cases in which the carcinoma was considered inoperable before scalene node biopsy, 5 (26%) had positive nodes (Table 3).

Thirteen patients in the series of 51 cases did not have pulmonary carcinoma. In two, with carcinoma of the breast and carcinoma of the stomach, the nodes were positive. The 11 negative biopsies were in 2 cases of granuloma of the lung; 2 cases of pulmonary tuberculosis; 1 case of middle lobe syndrome; 4 cases of inflammatory pulmonary lesions; 1 case of mediastinal lipoma, and 1 case of malignancy of the gastrointestinal tract.

Table 1.—*Prescalene Lymph Node Biopsy*

Total patients	51	
Positive right	4	
Positive left	5	
Total positive	9	(18%)
Patients with carcinoma of lung	38	
Positive right	3	
Positive left	4	
Total	7	(19%)

TABLE 2.—*Site of Pulmonary Carcinoma in Cases of Positive Scalene Biopsy*

Palpable		Nonpalpable	
Right upper	1	Right upper	1
Left upper	2	Right hilar	1
Left hilar	1	Left hilar	1

TABLE 3.—*Determination of Operability*

Considered operable before scalene biopsy	19	
Negative biopsies	17	
Positive biopsies	2	(10%)
Considered operable	19	
Negative biopsies	14	
Positive biopsies	5	(26%)

In summary, in 21 (55%) of the patients with pulmonary carcinoma the cancer was considered inoperable; in 8 (21%) exploration was performed but the cancer was inoperable, making a total of 76% in which the lesion was inoperable; 6 pneumonectomies and 2 lobectomies were performed, a total of 21% being considered operable.

DR. JOHN F. HIGGINSON, Portland, Ore.: I should like to congratulate Dr. Shields on his very interesting report and make some preliminary mention of the work of two of my associates at the Portland Veterans' Administration Hospital, where I am a consultant.

Since September, 1955, Dr. William C. Gardner, the full-time thoracic surgeon there, and Dr. Robert W. Kendall, one of the surgical residents of the hospital, have been doing bilateral scalene fat pad excisions in an effort to determine the incidence of scalene node involvement in proved cases of bronchogenic carcinoma with nonpalpable nodes.

[Slide] This shows the criteria they have set up for their bilateral fat-pad excisions. They decided that there must be roentgen evidence of a lung lesion, and that the patient must have no palpable cervical lymph nodes. Obviously, patients having palpable nodes had the usual biopsy.

[Slide] They have done bilateral fat pad excisions in 75 cases, and, of these, 50 have proved to be cases of bronchogenic carcinoma.

[Slide] Among the 50 cases of eventually proved bronchogenic carcinoma in which the nodes were not palpable and in which bilateral scalene fat pad excisions were done, 22% have been found pathologically to have metastically involved nodes. It must be pointed out that these figures are for all cases in which the tumor was eventually proved to be bronchogenic carcinoma. A division of cases into "clinically resectable and clinically nonresectable" will be necessary for comparison with the series reported by the authors.

This very creditable piece of work by Drs. Gardner and Kendall naturally makes one stop and think. In my own private practice I have not as yet adopted this routine screening procedure. Positive findings in cases of nonpalpable scalene nodes, or even in cases of palpable nodes, may perhaps now not always be a contraindication to radical pneumonectomy.

There is growing evidence that supervoltage therapy, such as that with Co^{60}, can sterilize readily accessible foci of lung cancer, and its use postoperatively in these instances should be considered. In fact, recently I have begun to refer certain selected patients for supervoltage therapy after radical pneumonectomy when the mediastinal nodes in the block specimen have been found to be involved. This irradiation is planned to cover the entire mediastinum, including the cervical mediastinum and the scalene fat pad areas.

In the treatment of the less favorable cases of bronchogenic carcinoma (and certainly there are many of these), resectional surgery or x-ray or drug therapy, or two of these, or all three, may be necessary and helpful.

DR. HARRY W. SOUTHWICK, Chicago: I have found Dr. Morfit's paper particularly intriguing, first, because this complication is, fortunately, most unusual and, second, because it is possible that at the present time certain medications may alleviate the necessity for surgical decompression when one is faced with such a problem.

In my own experience, I have found that with unilateral neck dissection and, generally, even with bilateral neck dissection, clinically significant increased intracranial pressure is an uncommon complication. An exception to this occurs when one performs a total thyroidectomy and bilateral paratracheal node dissection along with the bilateral neck dissection. I believe the edema here is ultimately traceable to the removal of the pharyngeal-digestive tube plexus, which Dr. Morfit mentions.

I was going to be one of those persons who "just happened" to have a slide in his pocket, but the slide is somewhat damaged, through the baggage handling by one of the airlines; so you will have to take my word for the appearance of the patient I should like to mention.

It was about a year ago that I operated on a man in his early 20's who had an advanced carcinoma of the thyroid with involvement of both lobes and bilateral neck metastasis. Twenty-four

TABLE 4.—*Disposition of Patients*

Inoperable	21	(55%)
Pneumonectomy	6	(21%)
Lobectomy	2	
Exploration	8	
Surgery refused	1	
Total	38	

hours following the indicated procedure, which included total thyroidectomy, bilateral neck dissection, bilateral paratracheal node dissection, and removal of nodes from the upper medastinum, the patient developed rather marked edema of the head, accompanied by the usual signs and symptoms of increased intracranial pressure. He was placed on intravenous prednisolone, and at the same time a decompression was performed. Three days later we gradually began to eliminate the prednisolone—and I am speaking of prednisolone in rather massive dosage. We were using up to 200 mg. a day. We gradually tried to wean him away from this medication, but by the seventh postoperative day he began to develop again, in spite of his decompression, signs of increased intracranial pressure.

He was placed back on prednisolone, and the dosage varied at this time from 50 to 75 mg. a day over a number of weeks. This controlled his symptoms, and for all practical purposes the site of the decompression was almost flat against the side of his head. His dosage over the course of the next few months was dropped to as low as 15 mg. a day, and by the middle of the summer we felt it was reasonable to restore the bone plate, which had been refrigerated since the time of its removal. Following replacement of the plate, there was a temporary increase in his intracranial pressure, accompanied by edema of the head and neck, but use of prednisolone again reduced this edema, and again the young man was gradually weaned away from the material.

It is now six weeks since he has had any steroid therapy; his bone plate is back in place, and he has no signs or stigmata of increased intracranial pressure of any degree at all.

Obviously, at the time Dr. Morfit was faced with this problem, the material which we have been able to use was not available. In retrospect, I doubt if in our own case the decompression contributed in any significant degree to the patient's ultimate recovery. I believe that, in the future, serious consideration should be given to this form of steroid therapy in the handling of such a problem, rather than decompression, which was utilized some years ago.

Dr. A. J. Herlitzka, Madison, Wis.: I would like to thank the discussants for their excellent contributions.

In regard to Dr. Sanborn's remarks, secondary metastatic masses were encountered in at least six cases, none of which was included in this particular series. These were suspected of being primary mediastinal tumors. However, for those resected, the ultimate prognosis was not improved.

Another problem has been the differentiation of primary lesions of the tracheobronchial tree and esophagus which have extended into the hilus, producing a mass. Negative diagnostic studies compelled one to do an exploratory thoracotomy, only to find the lesion arising from one of the above sources.

Also, I should like to warn you of blood vessel dilatation, which may simulate a mediastinal tumor on a chest x-ray. Four such patients were operated upon, only to find an aneurysm. One of these patients, unfortunately, died of an uncontrollable hemorrhage during dissection of a nonpulsating saccular aortic aneurysm.

In regard to Dr. Keeley's remarks, two lipomatous lesions were found. One was an unresectable lipoangiosarcoma in a patient who died three months after surgery. The second was an asymptomatic giant benign lipoma detected on a routine chest x-ray. The lesion was the size of a football and was resected with relative ease. Both lesions were in young patients.

Dr. Joseph W. Gale, Madison, Wis.: Anyone with a chest lesion should have a P. A. film and a lateral film at least once every year. Anyone 40 years of age should have a film every six months. I should like to cite one case.

An executive was checked in Madison in 1953. He had a routine P. A. x-ray film. No chest pathology was noted. A year later he went to Rochester and was checked. The result was negative. One year after that he came to the University Hospitals. He then had a large mass in the upper lobe on the left.

I wrote to Dr. Clagett, my friend in Rochester, and told him what we had found. He sent his x-rays to us. I didn't tell the roentgenologist in our institution what the problem was. He read the year-old Rochester films as negative. I did an exploration on this patient and found that the lesion was inoperable. In one year he had developed that large Pancoast tumor, which had become inoperable.

At Rochester and at Madison previously we had not taken a lateral film. The diagnosis probably could have been made on a lateral film. So I believe that when you get a P. A. chest x-ray, a lateral film should be ordered at the same time. These two views are much more valuable than a single one.

The same thing applies to the mediastinum. Many of these lesions lie in the midline, and one cannot see them on the P. A. film. In order to make a correct diagnosis, one must have a lateral or an oblique film.

I don't want to seem facetious, but may I ask how many in this organization or among the guests here have had a chest x-ray in the last six months? Eighty per cent. That is most com-

mendable. I don't know how often you have them taken, but I feel that once every six months is not too often, especially if one is over 40 years of age.

Another point: Mediastinal tumors are not common. It took us 18 years to accumulate this series. Of course, there were others admitted to the hospital on other services—with liposarcomas, etc.—who were treated by x-rays. They were not counted in this series.

Anytime that you want to put any tumor any place in the body, put it in the mediastinum. When this paper is published, you will see that we have noted an osteoma in the mediastinum. Please don't ask me where some of these tumors originate; but they appear there.

We are seeing approximately 500 chest cases a year on the chest service, and have accumulated only 174 mediastinal tumors in 18 years; so they account for less than 1%. This series shows that 25% are malignant. One must not watch and wait but should explore and identify these tumors and remove them before they become malignant or cause extreme mechanical difficulty.

DR. THOMAS W. SHIELDS, Chicago: Dr. Palumbo's results are in essential agreement with our findings. In a small group of patients with clinically nonresectable carcinoma of the lung, we obtained 3 positive node biopsies in 10 patients with nonpalpable scalene nodes. Thus, one can readily see that the inclusion of such patients will raise the positive yield of the procedure.

Dr. Higginson's report of bilateral biopsies is of interest, and his remarks regarding the possibility of proceeding with surgical resection in the face of a positive biopsy are provocative and stimulating. It is hoped that future studies of the fate of patients with metastatic disease in nonpalpable scalene nodes will clarify this phase of the problem.

Extralobar (Diaphragmatic) Sequestration of the Lung

EDWARD J. BERMAN, M.D., Indianapolis

The Latin verb *sequestrare* means to separate. The noun *sequestrum* has well-known orthopedic connotations and is defined in Stedman's "Medical Dictionary" as "a piece of necrosed bone which has become separated from the surrounding healthy osseous tissue." Pryce, in 1946, applied the term to a type of pulmonary pathology wherein the blood supply of a bronchopulmonary segment is derived from the aorta rather than the pulmonary artery. This bronchopulmonary mass could be enveloped by lung (intrapulmonary sequestration) or could exist outside an otherwise normal lung (extrapulmonary sequestration). In either case the idea of necrosis is not implied. There is a loss of bronchial connection (unless infection has caused erosion into a bronchus),[8] and a variable venous drainage exists in that blood may return via either pulmonary or systemic veins. An excellent review of the differences between intra- and extrapulmonary sequestration, as well as an explanation of the origin of these sequestrations, is that of Smith.[7] A review of the literature concerning the embryology of these conditions reveals sharp differences of opinion. Thus, Pryce held that the fundamental pathology was vascular in that a persisting systemic artery (i. e., from the aorta), by producing traction on a "bronchial tip of the embryonic bronchial tree,"[5] finally succeeds in producing separation or capturing it. Boyden, on the other hand, disagrees with this concept for three reasons. "First, accessory arteries to the base of the lungs occur in the absence of cysts, and vice versa." (These "cysts" occur, as the sequestered lung tissue is without a bronchus to drain away the mucus produced by the columnar epithelium.) "Second, the distribution of an accessory artery is often such that mechanically the artery could not have produced a traction defect. . . . Third, arteries do not exert traction upon viscera in developmental stages. Instead, there is either a gradual shifting of an artery along the wall of a major vessel like the aorta (either through differential growth or selection of plexiform channels), or new arteries develop successively to keep pace with a "descending" organ.[11] (The stomach originally arises from the cervical region of the embryo, but gradually it shifts its position along the ventral wall of the aorta until it receives the definitive celiac artery.)

Prof. T. W. Torrey, chairman of the department of zoology of Indiana University, feels that the origin of an accessory lobe represents no more than the potential for the production of supernumerary parts in the ordinary course of subdivision of the original primary bronchi. He calls attention to the fact that the original embryonic lung buds lie in a loose mesenchyme which is destined to become the mediastinum and that accessory lobes might well come to rest in any of the regions ultimately involving the mediastinum, for example, the diaphragm. Accordingly, one can visualize endless possibilities resulting just as a matter of chance—cysts, free or attached to the lung proper, embedded in the mediastinum, herniating through the diaphragm, etc. Whether such

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 21, 1957.

Assistance was given by Dr. Edwin E. Pontius, of the Department of Pathology, and Dr. Harold C. Ochsner and his associates of the Department of Radiology, Methodist Hospital; and by Dr. Paul V. Evans, Department of Pathology, and Dr. William A. Tosick, Department of Radiology, Indianapolis General Hospital.

an accessory lobe becomes a true accessory lung lobe or ends as a pathological mass depends on whether it retains any functional connection with the tracheobronchial tree. The characteristic systemic arterial supply is explained by the fact that the portion of the gut from which trachea and lungs will derive is supplied by a plexus of vessels representing the future dorsal aortae and that this plexus drains into the veins of the body wall. Ultimately special portions of this plexus are molded into the pulmonary system, but the mere fact that from the start there is an intimacy between pulmonary and systemic vessels provides abundant opportunity for abnormality of supply and drainage. Added to this is the general tendency for any displaced part to pick up the nearest handy blood supply. Thus, one need not be surprised at any vascular connections he sees.[10]

Diaphragmatic Hernia and Extralobar Sequestration

In Pryce's previously quoted article, appearing in 1946, one finds this statement: "There is a well known association between extralobar sequestration and diaphragmatic hernia which has not been noted with the intralobar type." Smith cites Bolck as offering this explanation [7]:

> As the left leaf of the diaphragm closes later than the right the changes of separate survival [of accessory lung root and primitive lung bud] are greater in the region of the left diaphragm and greatest if the left diaphragm is deficient and allows the separate mass further room to remain free.

This discussion is predicated on the theory that "the chance of separate survival depends upon the keeping of a distance between accessory and developing lung. Otherwise, there is incorporation within the normal lung at an early stage with normal development and no trace of separate existence." This, then, "explains the high preponderance of left-sided lesions in lower accessory lung (extralobar sequestration) and its association with congenital diaphragmatic hernia. Should the mass be incorporated . . . at a relatively late stage the condition of intralobar sequestration arises." [7] Pryce, writing again in 1947, with Sellors and Blair as co-authors, states [6]:

> Congenital diaphragmatic defects seem to result in the same way from ischemic traction on abnormal embryonic arteries running from the developing diaphragm to the developing lung. They are also most common toward the pulmonary ligament on the left side. They are, however, associated with lower accessory lung only when a detached bulbous tip survives. The fact that most diaphragmatic defects are not associated with a lower accessory lung indicates that these detached elements have a low survival rate.

The literature contains many references to this association of lower accessory lung and diaphragmatic hernia. Curiously, however, there seems in general to be no definition of just what is meant by diaphragmatic hernia. The commonest diaphragmatic hernia found in newborn infants is unquestionably the Bochdalek hernia. Yet it is unlikely that this is what is implied. Certainly, accessory lobe and developing lung would be more likely to be compressed in this instance than separated by the hernia. Is it right to assume that a defect in the diaphragm would permit an accessory lobe to maintain an independent existence? Or is it more logical to assume that the presence of an accessory lower lobe might physically interfere with the development of the diaphragm, thereby producing an eventration? I favor this latter explanation, and in the two cases with diaphragmatic extralobar sequestration upon which I have operated the diaphragm was the site of eventration. This is at least a special kind of hernia. By eventration we mean an elevation of the dome of the diaphragm, due, in this instance, to a weakening, thinning, and replacement of its muscle fibers.[12]

Report of Cases

Case 1.—A 7½-year-old boy came to the hospital because of repeated attacks of pneumonia and vague abdominal pain. He first began to complain of abdominal pain only two years preceding this admission, although he had always been a feeding problem. During the past year he had suffered many respiratory infections and four attacks of

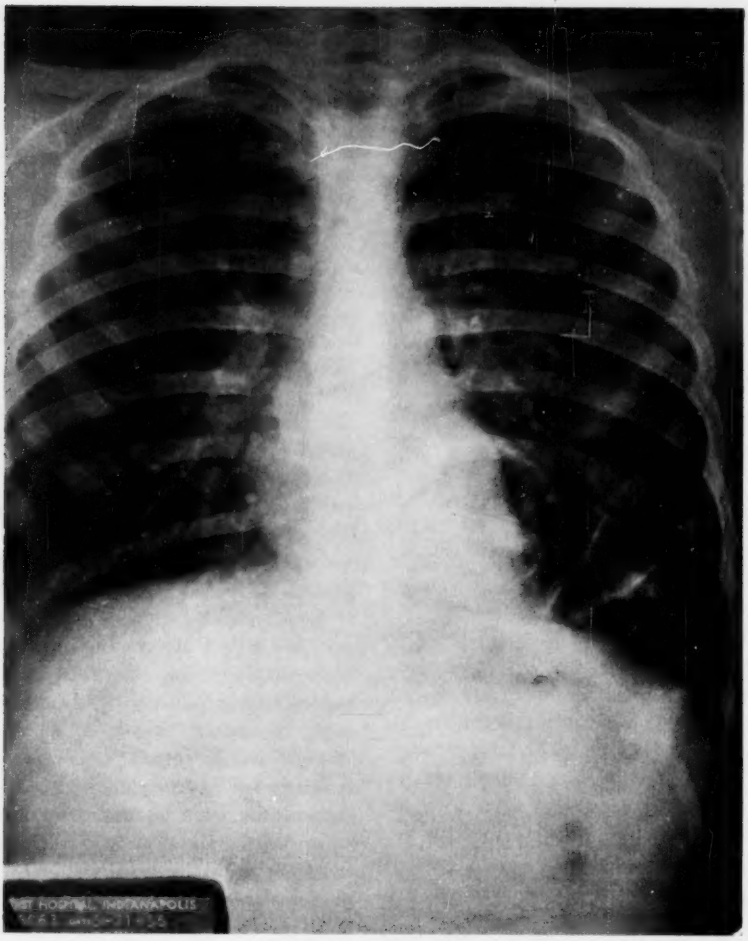


Fig. 1 (Case 1).—P. A. x-ray of chest revealing eventration of left side of diaphragm.

pneumonia. In each instance the pneumonia responded promptly to antibiotics. The patient was the product of an uneventful pregnancy. Birth weight was 8 lb. Physical examination showed that the child was well developed and well nourished, and there were no positive physical findings except for dullness to percussion and absence of breath sounds in the left base. The radiological studies, however, were interpreted as demonstrating a diaphragmatic hernia (Fig. 1). Repair was recommended, and the patient was taken to surgery. The incision was through the seventh interspace. The operative dictation is quoted verbatim: "The very large posterolateral hernia was immediately visualized, and we saw at once that the abdominal viscera were contained not only in the sac but under an attenuated diaphragm. The diaphragm was incised and the peritoneum opened. We were then able to free the colon and spleen from their adhesions, and the redundant portion of the sac was excised. The peritoneum was then closed with a purse-string suture of 00 Deknatel surgical silk. At this point we were able to direct our attention to repair of the diaphragm. We found that a portion of it was very definitely diseased, and this process was characterized by thickening and the formation of large lacunae, which contained a gelatinous material. Most of this was excised and sent to the department of pathology for examination. The only abnormality noted in the lung was a structural one, wherein the lower lobe was shaped to fit the hernia. With repair of the diaphragm through many sutures of 00 Deknatel silk broad areas of apposition were obtained. When

a normal contour had been reestablished, we found that a space was left in the posterolateral position, where the hernia had previously been. This is explained by the structural indentation of the lung, previously described. Because of this space, we felt that endothoracic drainage for a few days was indicated, and, accordingly, a small catheter was placed in the chest through the eighth interspace. The phrenic nerve was not disturbed, and good diaphragmatic motion was observed prior to closure. Penicillin and streptomycin were instilled into the chest, which was then closed in layers, using 0 chromic absorbable surgical sutures for pericostal closure and 00 chromic absorbable surgical sutures for the other layers. The skin was closed with 000 Deknatel silk. The patient tolerated the procedure very well and was returned to the ward in good condition. It was not necessary to give a blood transfusion in surgery."

The postoperative course was uneventful. The appearance of the chest taken on the first postoperative day is shown in Figure 2. We directed our efforts to interpreting the pathology we had encountered, which, as the reader gathers from the operative report, baffled us completely. Like the x-rays, the microsections are self-explanatory. They represent a multicystic mass with tall columnar, mucus-secreting, ciliated epithelium. There is very little muscularis in the walls of the cysts. No cartilage is seen. The tissue is unmistakably pulmonary in origin, and the final tissue diagnosis was "multicystic disease of the lung, congenital, with probable sequestration to extrapleural diaphragmatic location" (Figs. 3 and 4).

CASE 2.—A 3½-year-old boy was admitted to the hospital because of bronchopneumonia. The past

Fig. 2. (Case 1).—P. A. x-ray of chest taken on first postoperative day.

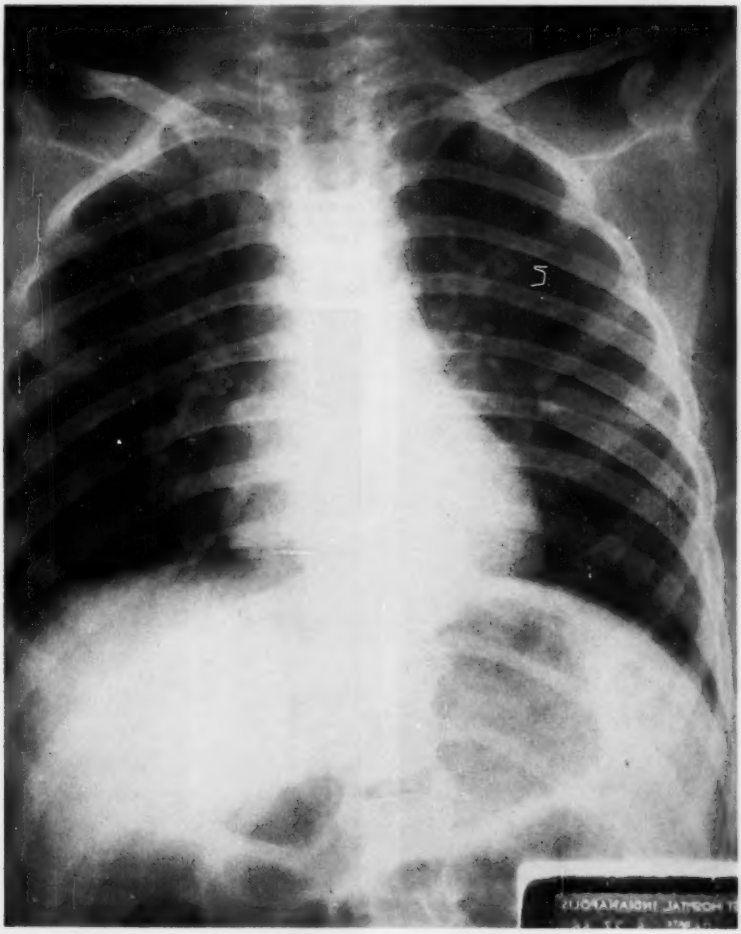


Fig. 3 (Case 1).—Photomicrograph of pathological portion of left side of diaphragm, representing multicystic mass of sequestered lung.

Fig. 4 (Case 1).—High-power photomicrograph demonstrating tall columnar, mucus-secreting, ciliated epithelium.

Fig. 5 (Case 2).—P. A. x-ray of chest revealing eventration of left side of diaphragm with displacement of heart to right.

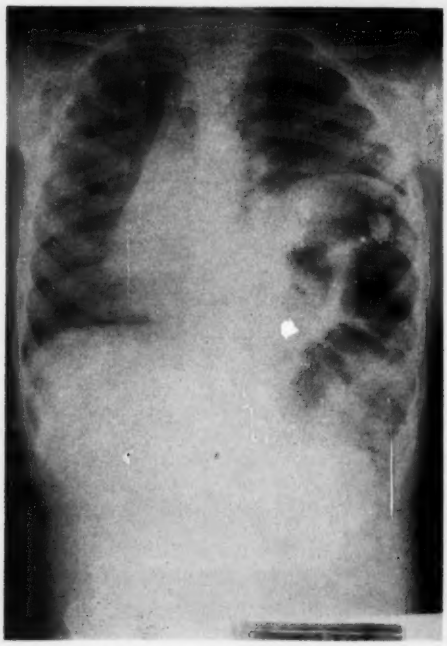
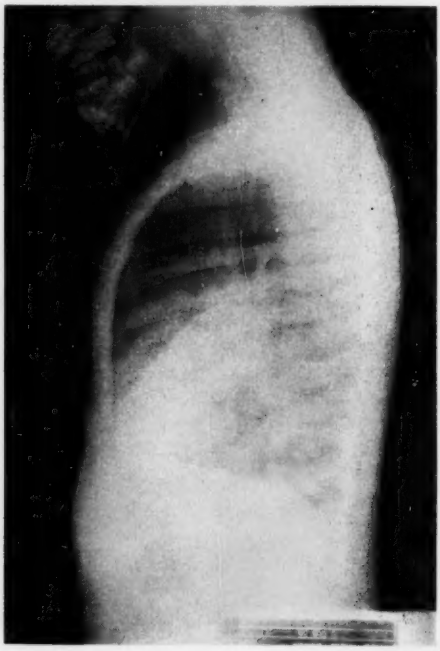


Fig. 6 (Case 2).—Lateral x-ray of chest revealing eventration of diaphragm.



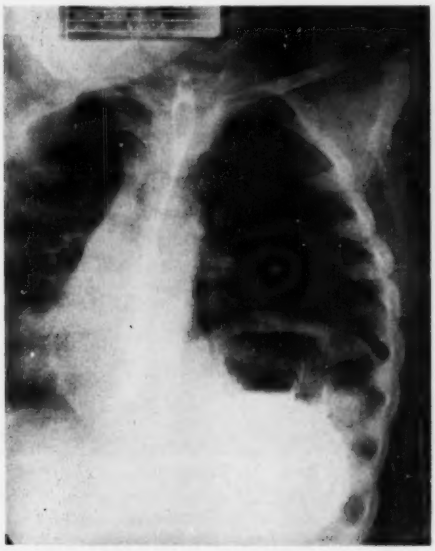


Fig. 7 (Case 2).—Barium swallow further illustrating the features of this eventration.

history revealed that the patient had suffered from frequent colds and cough. Since birth he had been noted to choke frequently while feeding and was said to be smaller for his age than his siblings. On physical examination the PMI was found in the fourth interspace 4 cm. to the right of the midclavicular line. The heart was otherwise normal. There was some decrease in excursion of the left side of the chest. There were dullness to percussion and diminished breath sounds in the left base. X-ray studies revealed a diaphragmatic eventration with displacement of the heart to the right (Figs. 5, 6, and 7). The diagnosis of

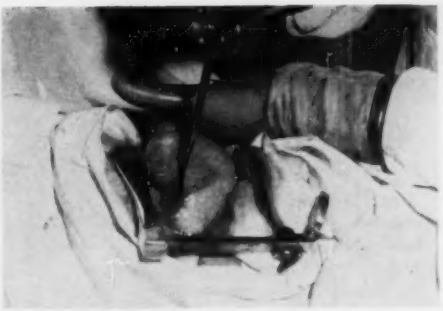


Fig. 8 (Case 2).—The sequestered piece of pulmonary tissue has been grasped with a Babcock forceps preparatory to dissecting it away from the diaphragm.

Fig. 9 (Case 2).—Further dissection of sequestration.

eventration was made, and it was suggested that this might be due to extralobar sequestration of the lung. As soon as the patient's pneumonia cleared, he was taken to surgery, and an intercostal incision was made through the eighth interspace. A large sac, which appeared to be attenuated diaphragm, filled the lower half of the left pleural

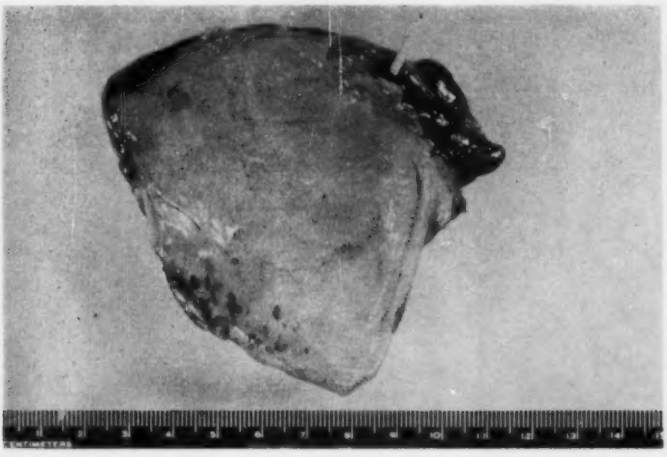


Fig. 10 (Case 2).—Sequestered "lung," pleural surface. The toothpicks mark the (systemic) blood supply.

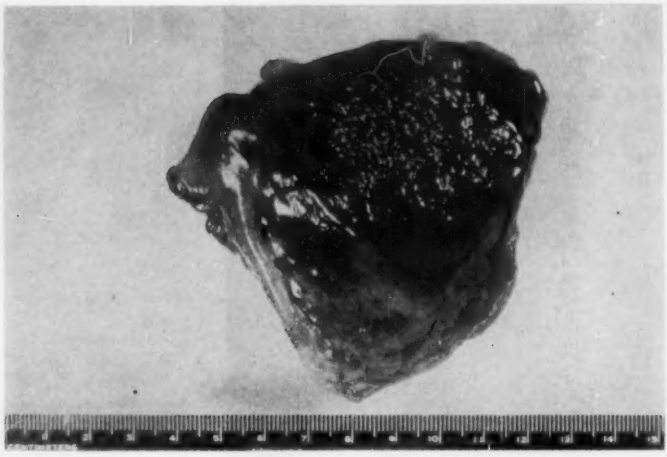


Fig. 11 (Case 2).—Sequestered lung, diaphragmatic surface.

space. Lying on top of this diaphragm, and intimately attached to it, was a mass of tissue approximately 1×5×4 cm. (Fig. 8). This appeared to be totally atelectatic lung tissue. At the medial aspect of this tissue, and entering it, were an artery and vein, both infradiaphragmatic in origin. The left lung itself was normal in all respects. The "sequestered" tissue was then excised with a small portion of the diaphragm (Figs. 9, 10, and 11). Two rows of silk sutures were used to repair the diaphragm, and normal movement was observed. The lung filled the pleural space well. The postoperative course was uneventful. The pathology report was that of extralobar sequestration of the lung. Sections of the artery supplying the sequestered tissue contained a large amount of elastic tissue and morphologically resembled the aorta (Figs. 12, 13, and 14).

Fig. 12 (Case 2).—Photomicrograph showing sequestration to consist of pulmonary tissue.

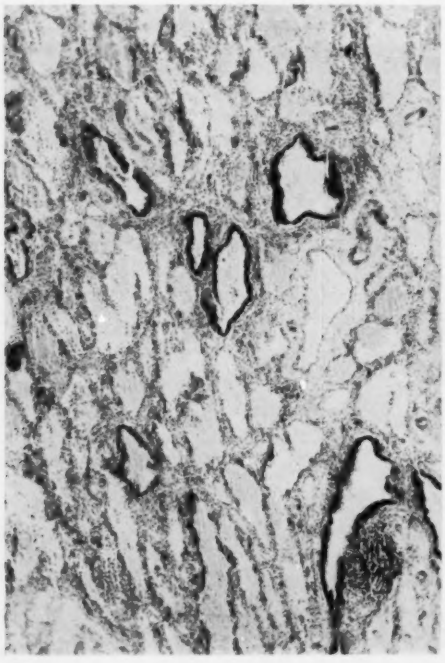


Fig. 13 (Case 2).—Section of arterial supply showing its aorta-like structure.

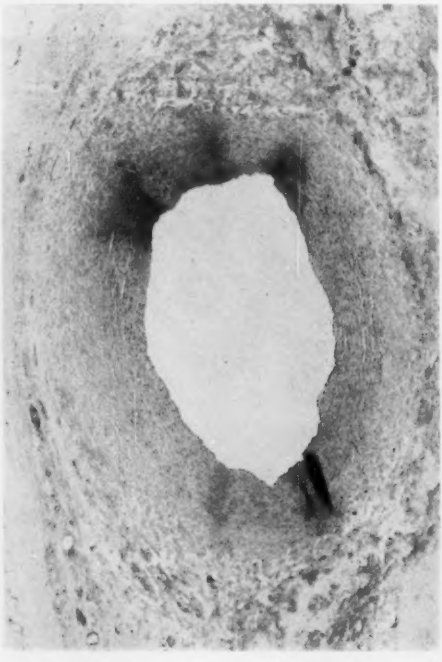


Fig. 14 (Case 2).—Elastic tissue stain of arterial supply.

Conclusions

These cases illustrate the problem of extralobar (diaphragmatic) sequestration of the lung. The diaphragmatic eventration clearly results from the sequestration. Embryologically this situation accrues from the production of supernumerary parts in the ordinary course of subdivision of the original primary bronchi, with ultimate displacement into and incorporation within the developing diaphragm. The characteristic blood supply derives from the original intimacy between pulmonary and systemic vessels and the general tendency for any displaced part to pick up the nearest handy blood supply.

Summary

1. Two cases of extralobar (diaphragmatic) sequestration of the lung are described.

2. The problem of sequestrations in general is reviewed.

3. A discussion of the pertinent embryology is given.

23 E. Ohio St.

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Respiratory Function in the Postoperative Patient

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Studies made on anesthetized patients indicate that an adequate volume of pulmonary ventilation and total absorption of carbon dioxide are requisites for the prevention of respiratory acidosis.[1] Oxygen desaturation seldom occurs in the presence of the high partial pressure of oxygen generally used with anesthetic gases. The altered physiologic state does not end abruptly when the patient leaves the operating room. The usual physiologic responses may remain obtunded by medicaments used preceding, during, and after operation. Blood loss, alterations in pressure relationships of the body cavities, and pain further alter the expected responses to the usual respiratory requirements, as well as the requirements themselves.

When the patient is again exposed to the ambient atmosphere, the partial pressure of oxygen is generally low as compared with that of the anesthetic gas mixture. The problem of oxygenation may supersede that of carbon dioxide elimination. We have attempted to evaluate respiratory adequacy during this phase of the patient's illness, the period following surgical operations.

Method

The subjects inspired room air through a Dighby Lee valve attached to a face mask. All expired gas was directed through a gas-mixing chamber and then through a dry test volume displacement gas flow meter. The mixing chamber contained a spring-activated fan to assure complete mixing and gas cocks for withdrawal of samples. Water-displacement calibration methods revealed an error of less than $\pm 2\%$ in volume measurements for the volumes and rates of gas flow encountered in this study.

Expired gas samples were collected in oiled syringes and were analyzed promptly in duplicate for oxygen and carbon dioxide content by the method described by Scholander.[9] All gas volumes were corrected to 760 mm. Hg pressure and 0 C temperature.

Arterial blood samples were obtained in heparinized syringes, to which a few drops of mercury were added for mixing, and were immediately placed in ice. Determinations of the pH were made promptly with a Cambridge glass electrode pH meter calibrated before each determination with standard buffer solution. The oxygen content, oxygen capacity, and carbon dioxide content of whole blood were determined using the manometric technique of Van Slyke and Neill.[14] Hemoglobin values were obtained on each arterial sample, using sodium carbonate dilution and photometric measurements. Frequent checks of the latter technique were made against oxygen-capacity determinations on the same samples.

The day prior to surgery base-line values for alveolar ventilation, pCO_2, arterial pH, base bicarbonate, and oxygen saturation were obtained. Similar determinations were made on all subjects at the end of the operative procedure immediately prior to endotracheal extubation while still in the operating room, 30 minutes later in the recovery room, on the morning of the first postoperative day, and at other selected times in the postoperative period. In seven patients, narcotics in average doses were administered immediately after the routine study on the morning of the first postoperative day and were reevaluated one hour following administration of the drug.

Clinical Material for Study

Patients were chosen because they were undergoing major abdominal or thoracic procedures, and not because of any impairment of their cardiorespiratory system (Table 1). The average age of this group was 60.8 years, the ages ranging from 38 to 88 years. No pulmonary resections were done, and several entries into the thoracic cavity were thoracoabdominal approaches for lesions within the abdomen.

The average operating time for all cases was 3 hours 42 minutes. All patients had intravenous

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TABLE 1.—*Types of Surgical Procedures*

Thoracic procedures		
Thoracoplasty	1	
Hiatal hernia	1	
Mitral valvotomy	1	
Esophagogastrostomy	2	
Exploratory thoracotomy	2	7
Abdominal procedures		
Comb. A. P. resection	1	
Epigastric hernia	1	
Anterior resection colon	1	
Cholecystectomy; common-duct exploration	2	
Exploratory laparotomy	1	
Subtotal gastric resection	2	8
Thyroid lobectomy	1	1
Total		16

thiopental (Pentothal) sodium, a muscle relaxant, endotracheal intubation, and inhalation of nitrous oxide and oxygen. Premedication varied with age, but usually consisted of appropriate dosages of meperidine and atropine, one hour prior to induction.

Computations

Alveolar ventilation (*Va*) was computed from the formula

$$Va = \frac{CO_2\ exc \times K}{CO_2\ alv \times BSA}$$

where *Va*=effective pulmonary ventilation in liters per minute per square meter body surface area; $CO_{2\ exc}$=amount of CO_2 excreted in liters per minute (minute volume×percent carbon dioxide in expired air); *K*=correction factor for standard temperature and barometric pressure; $CO_{2\ alv}$= fraction of alveolar gas made up of carbon dioxide (pCO_2 divided by 760); BSA=body surface area in square meters.

The partial pressure of CO_2 in plasma (pCO_2) was determined from the line charts of Van Slyke and Sendroy,[18] first converting whole blood carbon dioxide content to plasma content. Buffer base values were obtained from the nomogram of Singer and Hastings.[10] Arterial blood saturation was computed from oxygen content of whole blood, minus a standard 0.5 vol. % correction for oxygen dissolved in the plasma, divided by the oxygen capacity.

TABLE 2.—*Arterial pCO_2*

Case	Preop. Control	End of Operation	Recovery Room	First Postop. Day
1	36.8	82.0	60.2	46.0
2	43.0	38.0	39.5	30.2
3	30.8	31.1	35.2	30.4
4	41.0	34.9	34.2	33.0
5	36.5			53.0
6	46.5			48.2
7	42.0		47.5	50.0
8	33.6	23.2	44.0	53.0
9	42.5			35.0
10	47.5			35.3
11	47.5	35.0	62.0	51.0
12	37.8	61.0	42.5	51.5
13	48.5	53.0	52.0	49.8
14	44.0	47.0	42.5	45.6
15	52.0	78.0	92.5	58.0
16	42.0	62.0	53.9	53.5
Average	41.7	49.5	50.5	45.2
Median	43.0	47.0	44.0	48.2

Results

The average and median values of the pCO_2 are indicated in Table 2. Preoperative control values average 41.7 mm. Hg, while the average value at the end of operation was 49.5 mm. Hg. A further increase occurred in the 30-minute time interval between the operating room and the recovery room. In general the pCO_2 reverted toward normal except for one patient who had continued pCO_2 retention to a level of 92.5 mm. Hg (Patient 15). By the morning of the first postoperative day most values for pCO_2 were not significantly altered from preoperative control levels. The carbon dioxide retention during the surgical proce-

TABLE 3.—*Arterial pH*

Case	Pre-operative Control	End of Operation	Recovery Room	First Postop. Day
1	7.46	7.17	7.24	7.39
2	7.44	7.32	7.38	7.45
3	7.51	7.5	7.45	7.50
4	7.39	7.32	7.20	7.36
5	7.53			7.28
6	7.29			7.31
7	7.26	7.18	7.19	7.27
8	7.38	7.41	7.27	7.21
9	7.33			7.42
10	7.29			7.18
11	7.30	7.38	7.18	7.28
12	7.29	7.23	7.27	7.29
13	7.32	7.26	7.26	7.23
14	7.29	7.22	7.27	7.28
15	7.31	7.11	7.05	7.23
16	7.38	7.18	7.24	7.26
Average	7.36	7.28	7.25	7.31
Median	7.32	7.23	7.24	7.28

TABLE 4.—*Arterial Buffer Base*

Case	Preop. Control	End of Operation	Recovery Room	First Postop. Day
1	50	47.5	45.0	50.0
2	54	43.0	47.5	46.0
3	52	50.0	49.5	49.0
4	49.5	42.5	34.0	41.0
5	56			46.5
6	43.8			46.0
7	40.0		38.5	45.0
8	45.5	41.0	40.0	40.0
9	45.0			47.0
10	44.0			33.0
11	44.0	48.0	41.0	45.0
12	41.0	44.0	40.0	44.0
13	48.0	43.0	42.5	41.0
14	45.0	40.0	40.5	42.0
15	48.0	40.0	39.5	44.0
16	48.0	41.0	42.0	45.0
Average	47.1	43.6	41.7	44.0
Median	48.0	43.0	42.0	45.0

TABLE 5.—*Arterial Oxygen Saturation*

Case	Preop. Control	End of Operation	Recovery Room	First Postop. Day
1	90.8	87	94.8	99.5
2	94.8	123.1	95.0	88.1
3	97.5	102.2	92.4	93.8
4	96.1	84.7	72.0	91.2
5	89.6			74.5
6	97.2			75.0
7	101.0		108.5	93.5
8	118.0	108.2	100.5	78.7
9	85.3			88.6
10	90.2			88.5
11	101.0	114.2	90.7	99.0
12	87.6	109.1	84.1	87.5
13	90.2	104.1	90.1	86.9
14	97.2	107.2	89.4	90.3
15	94.0	112.0	98.5	90.2
16	93.0	112.1	88.6	90.5
Average	95.2	105.8	92.1	88.5
Median	94.8	108.2	90.7	88.6

TABLE 6.—*Alveolar Ventilation per Square Meter Body Surface Area*

Case	Preop. Control	Recovery Room	First Postop. Day
1	2.68		
2	2.03	1.26	
3	3.13	3.14	2.31
4	4.47	4.67	1.53
5	1.97		0.17
6	1.09		1.29
7	2.05	1.98	1.56
8	2.92	2.20	1.2
9	1.08		2.28
10	1.45		1.66
11	1.07	.92	1.48
12	1.94	4.04	
13	2.48	1.92	2.08
14	1.93	1.34	1.55
15	2.13	2.92	.91
16	1.65	1.44	1.04
Average	2.13	2.34	1.47
Median	1.94	1.98	1.55

dure when compared with control values of pCO_2 was significant when evaluated by the *t*-test ($P<0.1$).

Arterial pH values during these same intervals of study confirm acidosis during the operative procedure (Table 3). On the morning of the first postoperative day pH values were still below preoperative control levels. Comparison by the *t*-test showed this continued pH depression to be moderately significant ($P<0.05$). Arterial blood buffer base values (Table 4) indicate a metabolic acidosis occurred during surgery and was significantly persistent on the first postoperative day ($P<0.01$). In spite of the early correction of the pCO_2 values in the postoperative period, continued higher levels of fixed acids remained, and confirmed the decreased pH values which were present throughout the period of study.

Arterial oxygen saturation fluctuated through large ranges (Table 5). The average control value was 95.2%. At the end of the operative procedure the average was considerably higher; at this time all patients were receiving high partial pressures of oxygen. Hemoglobin was completely combined with oxygen, and increased amounts of dissolved oxygen were present in the plasma. A short time later in the recovery room, this oxygen excess was quickly lost, and average values were below control levels. Some values were depressed to extremely low and cyanotic levels. By the first postoperative day further oxygen desaturation occurred and coincided with depressed effective alveolar ventilation at that time (Table 6).

Seven patients whose average preoperative oxygen saturation was 97.2% (Tables 7 and 8) were given meperidine in doses of 50 to 75 mm. on the first postoperative day. These patients had alveolar ventilation determinations and arterial samples drawn just prior to administration of the narcotic, and again one hour following injection of the drug. In spite of the "depressant" action of the drug on respiratory centers, oxygen saturation was not significantly changed, but the effective alveolar ventilation was slightly increased.

TABLE 7.—*Arterial O_2 Saturation*

Cases	Preop. Control	First Postop. Day	First Postop. Day After Narcotic
3	97.5	93.8	93.2
4	96.1	91.2	84.9
5	89.6	74.5	74.5
6	97.2	75.0	98.6
8	118.0	78.7	85.0
9	85.3	88.6	88.5
14	97.2	90.3	91.5
Average	97.2	84.5	88.0
Median	97.2	88.6	88.5

TABLE 8.—*Alveolar Ventilation per Square Meter Body Surface Area*

Case	Preop. Control	Before Narcotic	After Narcotic
3	3.13	2.31	2.4
4	4.47	1.53	1.78
5	1.97	0.17	2.31
6	1.09	1.29	1.68
8	2.92	1.2	1.39
9	1.08	2.28	2.18
14	1.93	1.55	1.26
Average	2.37	1.48	1.86
Median	1.97	1.53	1.78

Comment

Many factors govern the physiologic response of patients undergoing surgical operations. The immediate postoperative period is often a critical time, during which many physiologic adjustments are made. Effects of anesthesia, sedation, disparity of blood loss and replacement, altered pressure relationships in the body cavities, partial or complete loss of organs, and age are all important considerations during this period.

Major surgical procedures are being undertaken in older people in proportion to the trend of increasing age of the population in general. Greater responsibilities rest on the surgeon, not only in his surgical judgment but in his decisions regarding postsurgical care. This is particularly true in patients with marginal cardiorespiratory systems. The immediate postsurgical state is frequently the period of cardiac and respiratory complications that influence the subsequent hospital course. A further understanding of the expected responses of patients during this time can enhance the standards of surgical care in and outside the operating room.

Postoperative oxygen desaturation is a prominent finding in this study. This occurrence can go unrecognized, for clinical cyanosis is consistently recognizable only when arterial blood saturation is in the range of 75%.[3] Arterial blood saturation can be accurately determined only by analysis of arterial blood, and is impractical for routine usage. In all patients some degree of oxygen desaturation was present on the first postoperative day, and in general is inconsistent with optimal conditions for response of the patient to the surgical procedure and eventual recovery.

Effective alveolar ventilation is often diminished by respiratory splinting due to pain, positioning, and frequently by large cumbersome dressings. Inherent changes of the alveolar membranes secondary to inhalant gases, and mechanical pulmonary distention, as well as tracheal edema secondary to intubation, are frequent sources of respiratory difficulties in the early postoperative period. These changes, which are most frequently quite subtle, can go unrecognized and leave the patient anoxemic for extended periods. Large doses of narcotics poorly timed often aggravate this respiratory deficiency,[11] but proper dosage at a time of maximum pain and apprehension can improve pulmonary ventilation. The fact that the patient can expel secretions with an effective voluntary cough also provides for greater ventilatory efficiency.

Respiratory acidosis accompanied metabolic acidosis throughout the period of study. Other investigators [1,7,5,12] have noted increased amounts of fixed acids during the surgical operation, but Holaday et al.[8] concluded that metabolic acidosis was an immediate response to carbon dioxide retention. In this group of patients decreased buffer base values were still present on the first postoperative day, in the presence of modest elevations of pCO_2. Metabolic acidosis not only accompanied the surgical operation but persisted into the early postoperative period. It appears that changes toward normalcy correlate well with the return of pCO_2 levels to normal ranges. Adequate alveolar ventilation in the postoperative period assures proper oxygenation, normal pCO_2, and diminution of the secondary metabolic acidosis.

Summary

1. Arterial oxygen desaturation was found in the postoperative surgical patient.

2. Respiratory acidosis was accompanied by a metabolic acidosis during the period of study.

3. Average, well-timed doses of narcotics improved alveolar ventilation and secondarily improved oxygen saturation on the first postoperative day.

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Reconstruction Versus Prosthesis

Observations in a Series of Fifty Cases

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Indications for Reconstruction

A series of 50 cases demonstrated that reconstruction is beneficial in the following conditions: (1) in nonunion of the neck of the femur; (2) when there is excessive absorption of the proximal and distal portions of the neck, so that only the head and the base of the neck and the intertrochanteric area remain; (3) in aseptic necrosis of the head as a consequence of dislocation of the hip, of fracture of the acetabulum, or of other injuries that interfere with the circulation of the head and neck; (4) in advanced osteoarthritic changes in the head of the femur; (5) when there are malformations of the head as a result of a shallow acetabulum or a long-standing pathologic condition of the hips, such as Perthes' disease or a slipped femoral epiphysis, and (6) in subcapital fractures in the aged. Subcapital fractures are so serious that some elaboration is in order here.

Subcapital Fractures. — The subcapital fracture is the one fracture in which the bone does not unite and in which aseptic necrosis occurs most frequently. The subcapital fracture patient of over 70 must have an immediate reconstruction operation. This may seem a radical statement until one realizes that all that elderly patients want is a satisfactory weight-bearing limb. Such patients are ideal candidates for arthroplasty of the hip with removal of the lesser trochanter. Many surgeons prefer the use of a replacement prosthesis, but I am of another opinion because of the well-recognized disadvantages [1] of prosthetic devices: (1) the absorption at the site of the metal and bone; (2) decalcification of the proximal portion of the distal femur; (3) loosening, and even breaking, of the prosthesis as a result of flaws; (4) soft-tissue contraction; (5) excessive scar tissue, and even bone formation, following extensive incisions of the ilium, and (6) individual susceptibility to metal and to resins.

The Case for Reconstruction: Advantages Offset Disadvantages

Relief of Anxieties.—From the patient's points of interest, reconstruction favors peace of mind regarding growth of bone, regarding whether or not union is taking place, and regarding lengthy duration. Neither the patient nor the surgeon need be concerned about metal sensitivity, as they are with regard to replacements, or about the possibility of fracturing the newly formed head.

Stability.—It is true that in some patients a slight Trendelenburg gait ensues but not always; in any case, that is neither disabling nor painful. Stability may be confidently anticipated.

By way of examples, two patients in the series under discussion suffered severe injuries after reconstruction had been accomplished: One (Fig. 1, Case 1) incurred an intertrochanteric fracture on the same side as the reconstruction without dislocation of the hip; the other (Figs. 2 and 3, Case 2) incurred a fracture of the supracondylar area

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Fig. 1 (Case 1).—A woman aged 49 suffered a fracture of the neck of the femur. Because of aseptic necrosis of the head, an arthroplasty was performed on Aug. 5, 1942. Subsequently the patient fell and sustained an intertrochanteric fracture, which did not cause a displacement or interference with the reconstruction. Fracture healed. The patient has been asymptomatic.

Fig. 2 (Case 2).—A woman aged 58 had had a fracture of the neck of the femur. Subtrochanteric osteotomy resulted in aseptic necrosis of the head of the femur and painful limitation of the joint. Reconstruction was accomplished. A year and a half later, the patient fell, sustaining a fracture in the supracondylar area of the left femur. Note the severity of the fracture. Although reduction is not perfect, functional result is satisfactory. The femur fractured below the reconstruction, but reconstruction was not disturbed.

of the femur on the same side as the reconstruction, again without disturbance of the reconstructed hip.

Relief of Pain.—One of the most consistent results of reconstruction is relief of pain, although some pain does recur from time to time. An unevenness in the newly formed head gives the sensation that the hip is going to dislocate. But those minor disturbances only last until the formation of fibrocartilage smooths the surface for articulation.

Slight Restriction of Flexion.—Some restriction of flexion of the thigh makes putting on and taking off shoes and stockings difficult, but this is not a grave drawback.

Activities Unimpeded.—On the whole, reconstruction is advisable, especially in the aged, whose activities, normally reduced in any case, are not further curtailed. One patient (Fig. 3, Case 3) in the series has been followed for 22 years, during which she has led an active life. Pain has recurred from time to time, as it does after any reconstruction or arthroplasty. Meticulous care in fashioning the head and in removing the posterior portion of the greater trochanter, which so frequently interferes with normal articulation with the acetabulum, prevented recurrent dislocations. Early weight bearing, approximately two weeks after surgery, is permissible in such cases provided a plaster cast has been applied. The total period of immobilization is six weeks.

Shortening.—In nonunion in which absorption of the proximal and distal portions of the neck has been severe, shortening of 1 to 2 in. will take place except in fresh subcapital fractures, in which shortening is usually only from ¼ to ½ in.

The Case For and Against Prosthesis

Indications.—Regarding prostheses, I am in complete agreement with Thompson,[2] who says that there are no absolute indications for the use of an intramedullary hip prosthesis but that there are justifiable in-

Fig. 3 (Case 3).—A woman aged 38 had had a fracture of the neck of the femur which resulted in aseptic necrosis of the head of the femur. Surgery was performed; a plastic cap was placed over the reconstructed neck. Because this cap disintegrated, it was removed. A reconstruction was accomplished. A roentgenogram (*B*) taken 22 years later demonstrates appearance of postoperative repair. The patient experiences some pain and discomfort from time to time, but the hip is stable. The knee joint is sometimes painful and has limited flexion, because of the position that was achieved with the cast at the first operation.

Fig. 4 (Case 4).—A woman aged 54 sustained a fracture in the mid-cervical area of the left hip (*A*). The next day, without the aid of conservative treatment, an open operation was performed and a stem prosthesis inserted, as seen in *B* and *C*. The patient currently (1957) has severe pain in the left leg, and is unable to step on the left foot; crutches are necessary at all times. Note the amount of sclerosis surrounding the head of the prosthetic femur (*C*).

dications: fractures in an aseptic necrotic head; radium necrosis fractures of the femoral neck; soft femoral heads in which (unless the shaft or recipient is too decalcified), because of either demineralization or metastatic malignancy, the fragments cannot be maintained with internal fixation; rheumatoid arthritic fractures of the femoral neck; cystic or malignant bone diseases; as a humane adjunct to nursing care in certain shock therapy fractures in mental patients and in terminal care of aged patients having pathologic fractures.

The Aged.—Recently, Shapiro [3] observed: Age in itself is not an indication for any particular form of treatment. . . . If the conditions are such as to preclude the possibility of a good result in a reasonable period of time, then we do not hesitate to advise the use of a substitution prosthesis. On the other hand, if the conditions are such as to assure the possibility of union and the securing of a good functioning hip from nailing, then the hip should be nailed regardless of the age of the patient.

This policy is sound. The local and systemic findings must be evaluated apart from the chronologic age.

It is true that in the aged absorption due to decalcification is a normal metabolic process; consequently, when a stem prosthesis is inserted, because of such absorption, the shaft will break. If it does not break at once on insertion, it will frequently break afterward, when the pin or intermedullary portion has been forced down the femur by weight bearing. Tilting is another complication when osteoporosis of the proximal portion of the femur has set in; moreover, in advanced osteoporosis the patient's weight

Fig. 5 (Case 5).—A man aged 78 sustained a fracture of the middle third of the neck of the left femur. Two days later an open operation was performed and a stem prosthesis inserted. Note calcification of the capsule, both superiorly and inferiorly, as seen in different positions of the limb. The patient experiences limitation of motion and pain in hip and is unable to bear weight without crutches.

becomes a consideration in deciding on the treatment to be instituted.

Hip prostheses, then, in my considered opinion, should be reserved for persons beyond the age of life expectancy in the interest of their comfort and because of the risk of complications should operation not be successful.

Fresh Fractures.—In my opinion prostheses should not be inserted in fresh cases. Many disagree. In fractures of the neck of the femur or in the midcervical area, for example, the opportunity for healing should not be denied. Internal fixation in the correct weight-bearing line to see whether union is going to occur is the proper conservative treatment. Union of bone in such a hip is certainly preferable to the insertion of any mechanical or metal prosthesis.

The Young.—I am also opposed to inserting prostheses in the young. Prosthetic devices are relatively new. Sufficient data have not been accumulated, notwithstand-

ing five-year reviews collected by the American Orthopedic Association, to warrant their indiscriminate employment in the young. When prosthetic replacements do not prove workable after their introduction, what recourse remains? Fitting the prosthesis to the acetabulum is difficult in the young. At present, only about five sizes are available. Obviously, that does not cover all the needs in attempting to accommodate the various sizes, depths, and circumferences of acetabula.

Pain is intractable after the insertion of prostheses. In two cases (Figs. 4-5, Cases 4 and 5) in the series under discussion, severe pain has persisted two years postoperatively. Sclerosis is present at the articulation. The patients use crutches at all times. Removal of the prostheses would mean shortening of about 3 in. Fusion would also result in a shortened leg. The only recourse, nevertheless, is either to attempt another prosthetic replacement or to fuse the hip in a shortened position.

Mechanical Failures.—Mechanical failures of prostheses—breaking, loosening, disintegrating, and pitting of the materials—have been well covered in other reports, including my own.[1] Plastic or Lucite heads especially present the danger of fracturing and of disintegrating. They have even been suspected of being carcinogenic.

It might be worth experimentation to see whether in selected cases among the young or middle-aged group cadaver bone might be utilized in replacement and whether such bone might grow. Bone-to-bone, rather than metal-to-bone might be advantageous and ought to overcome the objections to metal or plastic prostheses. As I have previously stated,[4,5] there is no metal, regardless of the type used, that will replace bone or act as a substitute for it with equal efficiency, notwithstanding the many practical applications of metal. The apparatus for replacement serves only as an internal splint to maintain alignment until new bone can form in amounts sufficient to carry the patient's weight. Recently Shapiro[3] summarized this point of view: "Whatever its advantages, the prosthesis has not as yet been developed which is quite as good as the living head and neck of the patient's own femur even though the anatomy be somewhat distorted."

Choice of Incision for Insertion of Prosthesis

It is generally accepted that the Gibson incision, which affords a posterior approach to the hip, is the most applicable for the insertion of a prosthesis; but, in my opinion, if one plans on pinning the hip, this is not the best type of incision, because the posterior capsule, which furnishes most of the blood supply, must be opened to reduce the fracture. This so interferes with the circulation that too often aseptic necrosis ensues. In making this type of incision, in the hope that if the head does not bleed, it will be feasible to proceed with a replacement prosthesis, the risk involved is too great. Moreover, one cannot safely ascertain from the roentgenograms, even in posteroanterior and lateral views, whether the fracture of the femur is transverse; furthermore, the roentgenogram does not demonstrate the exact type of fracture that is present. For those reasons, I believe that an anterolateral incision for the purpose of exploration is preferable. This enables the surgeon to see what type of fracture is present, to determine whether fixation is possible, and to decide which procedure is advisable for a particular patient.

I deplore the practice of arbitrarily using replacement prostheses in the first 70 or 80 cases and then trying flanges in the next 70 or 80 in order to compare results. The surgical procedure utilized should always be a selective one in terms of whatever is best for the patient immediately concerned and for that patient's bone after all factors have been evaluated.

Summary and Conclusions

In a series of 50 cases reconstruction proved preferable to prosthesis in the following situations in the aged: (1) in cases of nonunion of the neck of the femur with extreme absorption, from decalcification, of the proximal and distal portions of the neck; (2) in aseptic necrosis of the head following any injury interfering with the circulation of the head and neck of the femur; (3) in severe osteoarthritic changes; (4) in the presence of malformations, and (5) in subcapital fractures.

The advantages of reconstruction are (1) early weight bearing; (2) allaying of the patient's anxieties regarding growth of bone, eventual union, duration of waiting, metal sensitivity, and the possibility of a new fracture, and (3) relief of pain.

The disadvantage of a possible Trendelenburg gait is slight because it is not disabling. Some restriction of flexion of the thigh and varying degrees of shortening are minor consequences, compensated by the major advantage of enabling the patient to continue comfortably with his normal activities.

The insertion of prostheses in the young is opposed under all circumstances because (1) failure of treatment precludes successful alternative treatment later; (2) available prostheses are too limited in sizes to ensure accuracy of fit to the acetabulum; (3) postoperative pain from sclerosis at the articulation is intractable; (4) removal of prosthesis for relief cannot be effected without resultant shortening; (5) plastic or Lucite heads may fracture or disintegrate and are believed by some to be carcinogenic; (6) metal carries with it the problems of sensitivity and absorption at the points of contact.

In general, it may be said that replacement prosthesis may be utilized only when fixation is not practicable, when the patient is past life expectancy, or when the fracture is a true subcapital fracture which would not heal in any case. In those instances, by reconstruction or by insertion of a prosthesis, the patient can be made ambulatory in a shorter period than by internal fixation. When fracture occurs in the presence of malignancy, any procedure that will relieve pain, discomfort, and disability is justified.

The approach to surgery must be exploratory and selective.

It is interesting that there were no deaths in the entire series, nor were there any instances of infection.

Five cases in the series are illustrated. Their salient features, exemplifying points made in the article, are presented in the legends to the accompanying illustrations.

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Chemicals and Enzymes in Debridement of Thermal Burns

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Introduction

At the present time surgical excision of the burn eschar is the most effective means of preparation for skin grafting. However, it is often bloody and may result in shock unless blood replacement is adequate. Various chemicals and enzymes have been suggested for this purpose. These include pyruvic acid,[1] streptokinase and streptodornase,[2] trypsin,[3] and collagenase,[4,5] none of which has proved completely successful. Theoretically, since over 70% of the dermis is composed of collagen, collagenase should be effective. Difficulty in production and the inability to penetrate the eschar, composed of charred keratin, are the two factors limiting its usefulness. It occurred to us that if a compound could be found which would penetrate or destroy this charred keratin of the burn eschar, collagenase would probably prove to be an effective debriding agent. The results of experimental and clinical investigations designed to test the effectiveness of several chemicals and enzymes in the debridement of burns are reported herein.

Sherry[6] has shown that certain vegetable cathepsins have collagenase activity when used in an acid medium. Three vegetable cathepsins—ficin, papain, and bromelin—were tested on collagen by measuring the quantitative assay * of the hydroxyproline in the residue, as described by Neuman and Logan.[7] Since hydroxyproline constitutes a constant fraction of collagen, this method provides an accurate measure of the amount of undigested collagen, permitting calculation of the amount of collagen digested. The findings are recorded in Figure 1; the peak of collagenase activity occurred at an acid pH of 3 to 4.

The only known enzymes that will digest keratin are a proteinase in the intestine of the clothes moth larva[8] and the fungi of certain Actinomyces strains[9] and Microsporum gypseum.[10] Of chemical compounds the most effective keratolytic agent is salicylic acid.[11] It is most efficient when employed in an emulsion base. A 40% concentration of salicylic acid in a hydrophilic ointment base was used as a debriding agent.

Experimental Studies

Animals.—A standard burn was produced in anesthetized dogs by bringing the blue

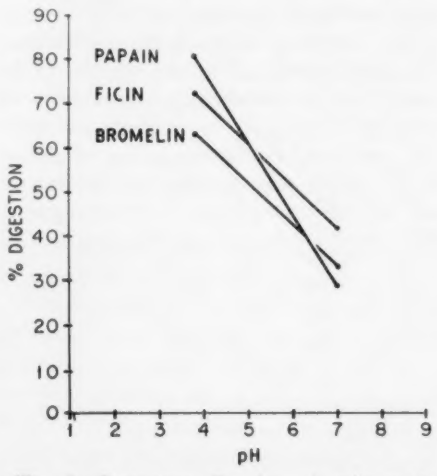

Fig. 1.—Percentage digestion of collagen by cathepsins at varying pH.

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* The collagenase assay was carried out by R. T. Hosie, M.D.

tip of the flame of a micro-Bunsen burner against the shaved hide for a period of 20 seconds. The chemicals and enzymes tested were applied to the burns. Pyruvic acid, acetic acid, hydrochloric acid, and hydrophilic ointment, which were used as bases, were also used as controls. Two applications of the test substances were made to the burns at 24-hour intervals. The effectiveness of debridement was assessed at 24- and 48-hour intervals.

Each of the three vegetable cathepsins was used in concentrations of 5% to 35% in hydrophilic ointment. Acetic, pyruvic, or hydrochloric acid was added to obtain a pH of 2-4. The mixtures varied in consistency from a watery solution to a thick paste. Although the results were not entirely consistent, the most effective enzymatic debriding agent appeared to be ficin in pyruvic acid with a pH of 3, used in the form of a thick paste applied for 48 hours.

Bromelin was discarded because of the unexplained death of three dogs following application of this enzyme to the burned areas. No satisfactory explanation for these deaths was found at autopsy. Preparation of a satisfactory mixture of papain is difficult because of the physical characteristics of this enzyme. It was therefore discarded when several trials indicated it was no more effective than ficin. No toxic effects followed the topical application of ficin. A solution of 5% ficin was given intravenously to one dog. After the administration of 25 cc. of this solution, the animal became dyspneic, developed bradycardia, and died. No specific cause of death was revealed at autopsy. Gross congestion of all viscera was noted.

When 40% salicylic acid in hydrophilic ointment was applied for 48 hours to the standard burn, in some instances the eschar was markedly softened. In others the eschar was found to be lying loosely over the burned area and was removed by merely lifting with gauze or with a hemostat. No bleeding ensued. To determine the amount of salicylic acid which might be absorbed from a burned area, 40% salicylic acid ointment was applied to a 10% burn in a dog. Serial determinations of blood salicylate levels at 8-hour intervals were done during a 48-hour period. The highest level observed was 6.5 mg. per 100 cc. When ficin and pyruvic acid paste or 40% salicylic acid ointment was applied to normal skin surfaces, no local tissue damage and no systemic ill effects were noted.

Humans.—Clinical studies were done in 14 patients with thermal burns, 1 with a decubitus ulcer and 1 with an ulcer secondary to a wringer injury of the hand. A portion of the burn was used as a control in all instances and was treated only with the suspension medium. The first patients included in the study were treated with ficin and pyruvic acid. The burns of later patients were first treated with 40% salicylic acid ointment applied twice at 24-hour intervals for a total of 48 hours. If debridement was not complete at 48 hours, ficin in pyruvic acid was then applied in the same manner for another 48 hours. All failures occurred early in our clinical experience. Since 1956, incident to the increased use of salicylic acid, we have had consistently successful results. In two patients, after application of 40% salicylic acid ointment, serum salicylate levels were determined every 8 hours for 48 hours. In the human, a 30-50 mg. level of salicylate per 100 cc. of serum is considered toxic. The highest salicylate level reached in humans was 15 mg. per 100 cc., falling to 4.8 mg. per 100 cc. in the next 48 hours. No clinical symptom, such as tinnitus, headache, diarrhea, dizziness, hyperventilation, tremors, or disorientation, was observed in any patient. In the one instance in which we applied salicylic acid paste to a raw granulating surface, the serum salicylate level rose to 4.4 mg. per 100 cc. in 24 hours, falling to 3.0 mg. per 100 cc. in 48 hours. However, it should be pointed out that the largest burn surface treated with salicylic acid has been 5%-6%.

The accompanying Table indicates the character of the eschar, the debriding agent

Results Following Use of Chemicals and Enzymes

Case No.	Date	Duration and Type of Eschar	Agent Used; Duration of Treatment	Result
1	1/10/55	Decubitus	15% ficin in 2% acetic acid in hydrophilic ointment; 48 hr.	Poor
2	2/4/55	Wringer injury; necrotic tendons	20% ficin in 3% acetic acid in hydrophilic ointment; 48 hr.	Poor
3	2/24/55	2 days Hard, dry, adherent	20% ficin in 2% acetic acid paste; 48 hr.	Fair
4	3/26/55	12 days Firm, adherent	Ficin in 2% acetic acid paste; 48 hr.	Good
5	4/21/56	21 days Firm, adherent	Ficin in pyruvic acid paste; 48 hr.	Excellent
6	7/16/56	11 days Hard, dry, adherent	40% salicylic acid in hydrophilic ointment, 48 hr. Ficin in pyruvic acid paste, 48 hr.	Excellent
7	7/20/56	15 days Hard, dry, adherent	40% salicylic acid in hydrophilic ointment Ficin in pyruvic acid paste, 48 hr.	Excellent
8	9/20/56	9 days Hard, dry, adherent	40% salicylic acid in hydrophilic ointment; 48 hr.	Excellent
9	12/27/56	11 days Soft, mixed 2d & 3d degrees; surgical debridement loose tissue 1 wk. prior to chemical treatment	Ficin in pyruvic acid paste, 48 hr.	Excellent
10	1/2/57	12 days Hard, dry, adherent	40% salicylic acid in hydrophilic ointment, 48 hr. Ficin in pyruvic acid paste, 48 hr.	Excellent
11	2/4/57	14 days Hard, dry	Ficin in pyruvic acid paste, 48 hr.	Poor
12	3/4/57	8 days Lt. arm; hard, dry Rt. arm; hard, dry, adherent	40% salicylic acid in hydrophilic ointment, 48 hr. 40% salicylic acid in hydrophilic ointment, 48 hr. Ficin in pyruvic acid paste, 48 hr. Ficin in pyruvic acid paste, 48 hr.	Excellent Good Good
13	9/7/57	8 days Soft, adherent	Ficin in pyruvic acid paste, 48 hr.	Poor
14	9/28/57	35 days Soft, adherent	40% salicylic acid in hydrophilic ointment, 48 hr. 40% salicylic acid in hydrophilic ointment, 48 hr.	Excellent Excellent
15	10/3/57	22 days Hard, dry	40% salicylic acid in hydrophilic ointment, 48 hr.	Excellent
16	10/10/57	21 days Hard, dry, adherent	40% salicylic acid in hydrophilic ointment, 48 hr.	Excellent

used, and the results obtained in the patients studied. A "poor" result means no debridement; a "fair" result, that a portion of the eschar disappeared under treatment; a "good" result, that only small removable fragments of dermis remained at the end of treatment, and an "excellent" result, that debridement was complete, with a wound

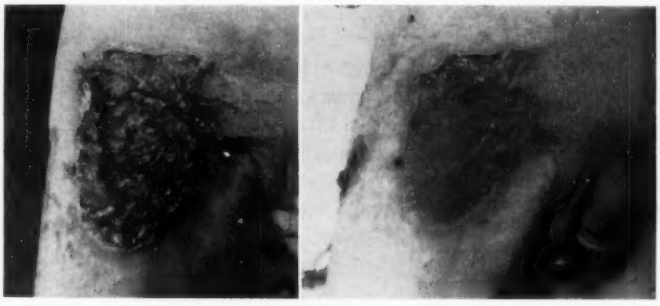

Fig. 2 (Case 7).—Left, before treatment; right, after treatment, with salicylic acid and ficin in pyruvic acid.

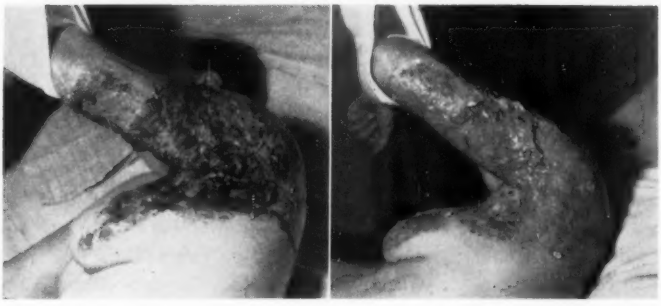

Fig. 3 (Case 8).—Left, before treatment; right, after treatment, with salicylic acid.

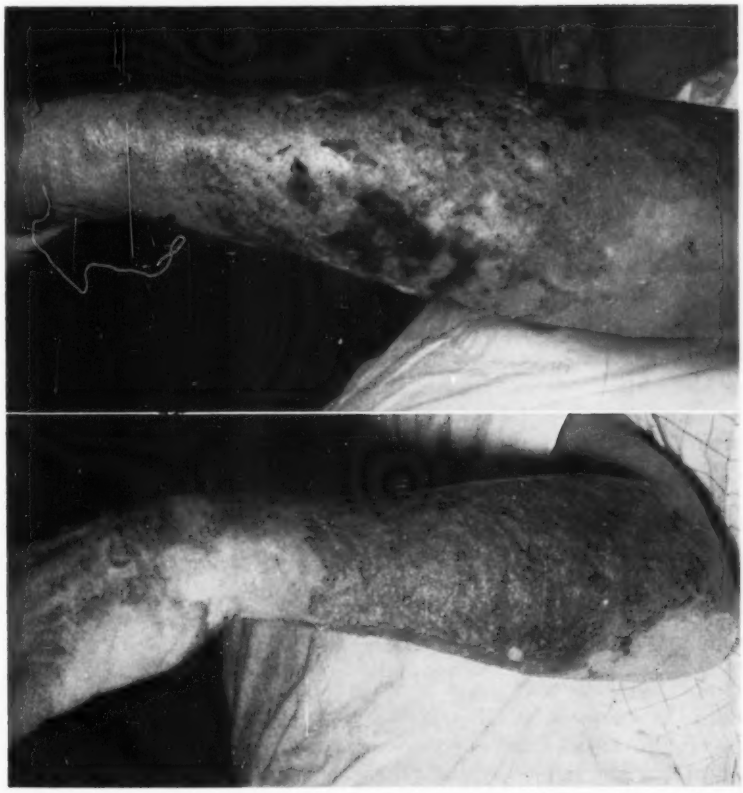

Fig. 4 (Case 15).—Above, before treatment; below, after treatment, with salicylic acid.

ready for grafting. Figures 2, 3, and 4 are examples of results before and after treatment, using the agents described.

Comment

With the demonstration that a cathepsin displays collagenolytic action when suspended in an acid medium, it appeared likely that it could be substituted for the collagenase derived from Clostridium histolyticum. It had the advantages of being readily available, inexpensive, and nontoxic. With pyruvic acid as a suspension medium, which itself is a swelling agent and denaturant of collagen, it seemed probable that the combination would be even more effective. However, many disappointments ensued. Under the impression that the observed failures were probably related to the inability of the mixture to penetrate the burn eschar, it seemed reasonable to incorporate a keratolytic agent in the study. Forty per cent salicylic acid was used for this purpose. Much to our surprise, we found that 40% salicylic acid by itself acts effectively, in many instances, as a debriding agent without the addition of cathepsins. At the present time we apply 40% salicylic acid in hydrophilic ointment to the burn eschar twice at 24-hour intervals. If debridement is then not complete, ficin mixed in pyruvic acid with a pH of 3 in the form of a paste is then applied in the same manner during the next 48 hours. In almost every instance a nearly complete bloodless debridement results.

No suggestion of toxic effects has been observed from the use of salicylic acid. Blood serum salicylate levels have not reached toxic levels. However, we have not

used this ointment on large burn surfaces, in which case absorption might be sufficient to produce salicylate poisoning.

Some pain is experienced on application of these agents. This is usually maximal at the time of the initial application. Salicylic acid ointment causes more discomfort during the application than the ficin-pyruvic acid mixture because it has a firmer consistency; once applied, it causes less discomfort than ficin in pyruvic acid. The pain from ficin in pyruvic acid usually subsides in three to four hours. The pain has never been severe enough for a patient to request removal of the ointment or to necessitate use of a narcotic. Ficin, when mixed with pyruvic acid, is dark brown in color and has a disagreeable, pungent odor. Salicylic acid ointment has no odor and is white in color. In no instance did the application of these agents unfavorably influence the subsequent "take" of skin grafts applied to the granulating surface.

Summary

Debridement of burn eschars has been achieved using 40% salicylic acid in hydrophilic ointment and ficin in pyruvic acid.

The chemical background and mode of action of these agents are discussed.

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Effect of Mechlorethamine Hydrochloride (Nitrogen Mustard) on Healing of Abdominal Wounds

S. M. FARHAT, M.D.; N. S. AMER, M.D.; D. S. WEEKS, B.S., and M. M. MUSSELMAN, M.D., Omaha

Cole and others[1,2] have used sterile mechlorethamine hydrochloride N. F. (nitrogen mustard) and drugs of similar action at the time of operation for cancer to discourage the local or distant implantation of malignant cells. These cytotoxic drugs may have an inhibitory effect on all young and proliferating cells. Therefore, it is logical to assume that these drugs might interfere with wound healing by inhibiting fibroblastic proliferation.

We have studied the effect of mechlorethamine hydrochloride on the healing of abdominal wounds in rats. The results suggested that this drug reduced the tensile strength of the wounds.

Material and Method

Preliminary studies in 18 rats suggested that mechlorethamine HCl interfered with wound healing. The following experiment was then designed.

Rats of mixed sexes, weighing from 132 to 215 gm., were selected. Under ether anesthesia, the abdomen was shaved, and with aseptic technique an incision was made in the midline through all layers of the abdominal wall. The incision then was closed with interrupted through-and-through 00000 silk sutures. Three groups of animals were studied (Table). In Group I, 19 rats were given a single dose of 0.6 mg/kg. of freshly prepared mechlorethamine hydrochloride * into the vena cava just before closure of the incision. These animals were allowed food and fluids ad lib after operation. In the preliminary studies it was observed that animals receiving mechlorethamine HCl had lost weight. Therefore, in Group II, 14 rats were operated upon and then partially starved to induce weight loss comparable to the weight loss noted in the mechlorethamine HCl group. Food intake was not measured. In Group III, 18 rats served as controls. These animals were operated upon in a similar fashion, but they were not given mechlorethamine. Food and fluids were allowed ad lib.

After seven days all animals were killed, and a segment of the abdominal wall, containing 1 in. of the incision, was excised. The sutures were removed, and the tissue was placed between two clamps and suspended, as shown in Figure 1. Water was run at a constant rate into the plastic bag attached to the lower clamp. The weight of the water causing the disruption of the wound was taken as the tensile strength of the wound.

The selection of a seven-day postoperative interval was designed to permit passage of the normal lag period of healing. Carrel[3] and Howes[4] demonstrated that rapid wound healing takes place from the fourth to the seventh day.

Sections of the wound margins were obtained for histologic studies.

Results

The results are shown in the Table. The animals receiving mechlorethamine HCl lost an average of 39 gm. in weight after operation. They had wound tensile strengths ranging from 500 to 1400 gm. The average strength was 846 gm. (median, 825 gm.). All the animals in this group showed marked irritability.

The animals on a restricted diet had an average weight loss of 53 gm. Their wound tensile strengths ranged from 550 to 1050 gm., with an average of 740 gm. (median, 750 gm.). This group also showed marked irritability.

The animals in Group III, or the controls, gained an average of 5 gm. after

This study was supported by Chas. Pfizer & Company, Inc.

From the Department of Surgery, University of Nebraska College of Medicine.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

Dr. Amer is now a resident in surgery, State University College of Medicine, Downstate Medical Center, 450 Clarkson Ave., Brooklyn 3.

* Merck Sharp & Dohme provided the mechlorethamine hydrochloride (nitrogen mustard) used in this experiment as Mustargen hydrochloride.

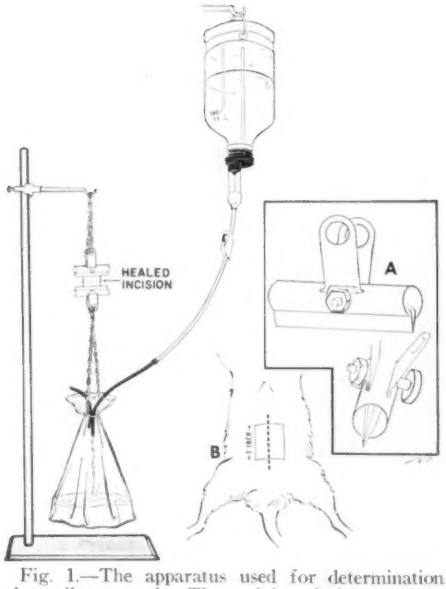

Fig. 1.—The apparatus used for determination of tensile strength. The weight of the water in the plastic bag that caused wound disruption was taken as the tensile strength of the wound.

operation. They had wound tensile strengths ranging from 900 to 1850 gm., with an average of 1295 gm. (median, 1400 gm.). Their postoperative course was uneventful.

The distribution of the animals in relation to tensile strength of their wounds is shown in Figure 2. The wounds of the animals receiving mechlorethamine had a tensile strength similar to that of the animals on a restricted food intake. The tensile strength in both groups was reduced as compared with that of the controls.

Weight Loss and Reduction of Tensile Strength as Found in Animals Receiving Mechlorethamine Hydrochloride (Nitrogen Mustard) and in Animals on Restricted Diet

Group	No.	Weight Change, Gm.	Tensile Strength, Gm.
Mechlorethamine (0.6 mg./kg.)	19	−39	846
Food restriction	14	−53	740
Control	18	+ 5	1295

In general no significant difference was noted in the appearance of the wounds. The wounds of the animals on restricted food intake showed more crusting and localized infection. The wounds of two of the rats in this group separated, and the animals died before the end of the experiment.

Histologic examination of the sections obtained from wound margins revealed no essential difference in the three groups. We could demonstrate no decrease in the number of fibroblasts in the mechlorethamine or the starvation groups.

Comment

Gilman and Philips,[5] Rhoads,[6] and Jacobson [7] described the cytotoxic effect of mechlorethamine on lymphoid tissues. These

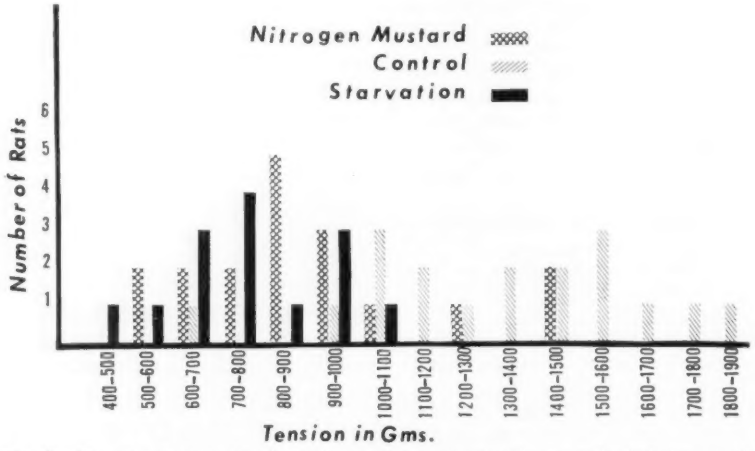

Fig. 2.—The distribution of animals in relation to the tensile strength of their wounds.

observations prompted the use of this drug in the treatment of malignant lymphomas. Because of its nonspecific cytotoxic effect, mechlorethamine has been used to treat other types of cancer. Recently Cole and his associates [1,2] have used it at the time of operation for cancer to reduce the chance of implantation of cancer cells.

Mechlorethamine hydrochloride is believed to inhibit the multiplication of proliferating cells by reactions with nucleic acids. This reaction leads to arrest of mitotic division in an early phase with nuclear fragmentation.

We wondered whether mechlorethamine hydrochloride might delay the healing of operative wounds in patients by interfering with fibroblastic proliferation. We found that the tensile strength of seven-day-old wounds was reduced in rats receiving mechlorethamine HCl. But these animals also lost weight. Animals on a restricted diet with a loss of weight comparable to that of the animals receiving mechlorethamine HCl showed a similar reduction in the tensile strength of operative wounds. This raises the question whether mechlorethamine HCl interfered with wound healing directly or whether it reduced wound healing indirectly by interfering with nutrition.

Summary and Conclusions

Mechlorethamine hydrochloride (nitrogen mustard) has been given to patients during operations for cancer to discourage the implantation of cancer cells. This drug is a nonspecific cytotoxic agent that affects all rapidly proliferating cells. We found that mechlorethamine hydrochloride interfered with the healing of abdominal wounds in rats. We could demonstrate no interference with fibroblastic proliferation. Mechlorethamine hydrochloride also resulted in weight loss in rats. Food restriction with a comparable weight loss interfered with the healing of wounds to a similar degree.

From these findings, we anticipate that the administration of mechlorethamine hydrochloride may interfere with the healing of wounds. We do not know whether mechlorethamine directly affects the elements of wound healing or inhibits wound healing indirectly by causing malnutrition.

University of Nebraska College of Medicine (Dr. Musselman).

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DISCUSSION

ON PAPERS BY DRS. SAUTTER, BUCKWALTER, AND ZIFFREN AND DRS. FARHAT, AMER, WEEKS, AND MUSSELMAN.

DR. DOUGLAS W. MACOMBER, Denver: I feel inadequate to discuss current research and its results upon debridement, other than surgical, of burn eschars. Under my observation, preparations containing salicylic and pyruvic acid have caused discomfort. Enzymatic preparations, such as streptokinase-streptodornase (Varidase), in solution entailed more nursing service than we could arrange. However, this same substance in a water-soluble jelly has been helpful, particularly in deep electrical burns. In these instances it has caused solution and separation of necrotic tissue at an accelerated rate. Upon the surface of eschars over cutaneous third-degree burns, it has been ineffective, except occasionally about the edges to start a

plane of cleavage, where surgical debridement could be started, with or without sedation or anesthesia.

I wish to compliment Dr. Sautter and his coworkers on research which may lead to further discovery or perfection of substances which will attack necrotic tissue while remaining harmless and painless to viable tissues. Since the third-degree burn results in progressive local and systemic disability, agents which will save days or weeks of morbidity and discomfort will constitute a long step forward in our therapy of burns. What we really need are synthetic socially and esthetically acceptable maggots!

DR. B. C. KILBOURNE, Chicago: The authors have shown some very nice work in this important phase of the treatment of burns. The difficulty in evaluating the depth of a burn makes it very hard to judge results of such work on a clinical basis. I assume that the burn depth in the experimental work has been carefully controlled in order to make comparison of the different methods valid.

I should like to ask Dr. Sautter how soon after the inception of a burn he uses the salicylic acid preparation in the treatment of the clinical cases.

DR. MICHAEL L. MASON, Chicago: The results that Dr. Sautter showed are certainly excellent. He has attacked one of the most difficult problems we have in the care of burns; that is the early removal of sloughed tissue.

I wonder if we are getting into the same position with the question of enzymatic and chemical debridement of burns that we were in a good many years ago, trying to find an antiseptic that would not harm living tissues but would harm just the dead tissues and bacteria.

I wonder what the next 15 or 20 years will show in relation to chemical debridement.

DR. JAMES BARRETT BROWN, St. Louis: If as many as two surgeons get together and start talking about burns, there usually is an argument.

Our basic philosophy has been to get the area as clean as possible, as soon as possible, and to restore what skin has been lost. This aims at getting a closed wound at the earliest possible date, as has been so well and earnestly advocated by Dr. Mason. The present authors are to be commended on their efforts in this direction.

They are also taking some onus upon themselves over those who advocate regarding burn eschars as inviolate membranes, and who say the membranes should have nothing whatever done to them. Perhaps most people have forgotten tannic acid by now, but it is still extant in the literature. Only last week, in a surgery meeting, a man was still advocating 10% silver nitrate applications, even for tiny babies who are burned, regardless of what extra damage might be done to the raw tissue.

As to the salicylic acid, the authors have shown results that look very good, and this work should be continued by them.

I wish also to commend them on thinking of salicylic acid, because that is one drug I can usually remember.

DR. WALTER CAMPBELL MACKENZIE, Edmonton, Alta., Canada: I should like to direct my discussion to the second paper, by Dr. Amer and Dr. Musselman and their colleagues. This subject is of interest to all of us who either are at the moment combining chemotherapy with the surgical excision of cancer or hope to do so in the future.

The question posed by their conclusion, that healing of wounds may be influenced by chemotherapeutic agents, is interesting and raises the point as to whether or not we can do something to counteract this influence. We have been interested in the question of wound healing, and have recently investigated the influence of norethrandrolone (Nilevar), an anabolic compound, and its effect on the healing of wounds. I should like to show one or two slides.

[Slide] This shows the effect of norethrandrolone on the healing of abdominal wounds in rats. We have compared the tensile strength of the wound itself with the pressure required to disrupt the intact abdominal wall in each individual case. As you can see, in the untreated animals five days postoperatively it takes a 6 lb. pressure to rupture the wound, whereas it takes 53 lb. to rupture the abdominal wall, and so on. At the 10- and 15-day periods a distinct difference in the results obtained from treated and untreated animals is noted. This has led us to devise a new experiment in which we will attempt to counteract the delay in healing produced in wounds by chemotherapeutic agents.

[Slide] This shows the method we use. It consists essentially of a cylinder over which the abdominal wall is stretched and clamped down in an air-tight manner. Air is allowed to escape into a cylinder and eventually will cause disruption of the wound. The pressure at which this occurs is read on a self-registering gauge. The intact abdominal wall is then disrupted in a similar fashion and the first result expressed as a percentage of normal.

It may just be that some anabolic compound of this kind may be of value in counteracting the action of chemotherapeutic agents as outlined by Dr. Musselman and his colleagues.

DR. SIDNEY E. ZIFFREN, Iowa City: Dr. Macomber asked how much discomfort occurs after the use of salicylic acid. There is a considerable amount of discomfort when it is applied, but very shortly it disappears, in sharp contrast with pyruvic acid, with which the discomfort lasts three to four hours. None of the patients required a narcotic to relieve the discomfort.

Dr. Kilbourne asked at which stage this material was used. In humans we do not use it before the 8th day, in most in 10 to 14 days.

In dogs, of course, all lesions were third-degree burns created by the flame of the Bunsen burner. In humans we have to assume that after 10 to 14 days, if the eschar is still present and the area is not healing, the burn is a third-degree one, and that is the kind we treated.

In response to Dr. Mason, we have not observed harm to normal tissue after use of salicylic acid, but we have not used it longer than 48 hours. There is a strong possibility, of course, that salicylic acid will harm normal tissue after that period of time. We do feel that proper treatment is early grafting of the area, and that is one reason why we haven't used it on large burn surfaces; we didn't want to jeopardize the patient until we knew more about it.

I appreciate the remarks by Dr. Brown in that respect also, for salicylic acid does some astonishing things. We obtained the idea from dermatologists. We asked them what, in their opinion, was the most powerful keratolytic agent, and they said salicylic acid. They felt the greatest concentration possible in miscible form was 40%, and that is the strength we used.

It is entirely possible that one can use a lower concentration, but I don't know. Neither do we know why it works, basically. We also do not know how large a body surface area covered by burn eschar one can treat without producing salicylate poisoning.

There may very well be other agents just as effective as salicylic acid, or perhaps even more effective. One that comes to my mind is sodium sulfide, which was one of the prime ingredients of depilatory agents before they became refined.

I think it is important not to concentrate all our efforts at the present time on the collagen of the dermis, but to pay a little attention to the keratin of the epidermis. I hope this presentation will stimulate others in this direction, because, as Dr. Brown hinted, this would prove a great aid in the treatment of patients who have been burned.

Retention of Normal Contralateral Kidney vs. Repeated Extracorporeal Hemodialysis

Experimental Study on Recovery of Ischemic Kidney

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The possible influence of distorted plasma and fluid composition of tissue on the recovery of damaged kidneys is of concern in the management of acute renal failure and has a distinct bearing on the application of extracorporeal dialysis in this condition. We sought in this study to evaluate the results of repeated hemodialysis applied to dogs rendered uremic by severe experimental renal damage.

Renal ischemia produced by occlusion of the renal artery has been shown to produce a lesion resembling that of the so-called crush syndrome, described by Oliver as acute ischemuric tubular necrosis.[1] In our hands, three hours of arterial occlusion, associated with the division of capsular vessels and perirenal sympathectomy, was followed by the spontaneous recovery of function of the kidney so treated. Van Slyke has reported a similar experience.[2] Six hours of occlusion under these conditions was followed by almost total infarction of the kidney in our dogs.

Recovery of function following four and one-half hours of unilateral (left) renal artery occlusion was studied in two groups of four dogs each. In the first group, the right kidney was removed at the time of occlusion of the left renal artery. Each of the four dogs died within six days. In the second group, the right kidney was left intact but was removed three weeks after occlusion of the left renal artery. Two of these dogs survived and were killled for necropsy three weeks after excision of the right kidney. Blood samples from each dog at this time contained 212 and 60 mg. of urea per 100 cc. The other two dogs died five and six days, respectively, after removal of the right kidney.

The results indicated that retention of the right kidney permitted an appreciable functional recovery of the left kidney during the three weeks following four and one-half hours of occlusion of the left renal artery. Histologic examination of the damaged kidney in the two dogs that died showed the damage to be too extensive for recovery to reach the threshold of function compatible with life. In a few regions, however, microscopic regeneration of tubular epithelium could be seen. In the surviving two dogs considerable regeneration of tubules had occurred, though within these areas patches of tubulorrhexis were evident.

The lesion produced by this period of occlusion was then employed in a comparison of degrees of recovery achieved either by retention of the normal kidney or by repeated extracorporeal hemodialysis.

This comparison was made in two groups of dogs. In the first group, each dog was subjected to occlusion of the left renal artery for four and one-half hours; the right kidney remained intact. Each dog was

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957

Linwood D. Keyser Fund Fellow in Surgical Research, Mayo Foundation (Mr. Edwards). Section of Biochemistry (Dr. Maher); Section of Surgical Research (Dr. Grindlay); Section of Urology (Dr. Thompson), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Occlusion of Left Renal Artery: Simultaneous Right Nephrectomy Followed by Repeated Hemodialysis

Dog No. Weight, Kg.	Dialyses	Fluid Used to Fill Dialyzer	Dialysis: Days After Onset of Ischemia	Blood Urea, Mg. per 100 Cc.		Period of Dialysis, Hr.	Fate of Dog	Weight of Kidneys, Gm.	
				Initial	Final			Left	Right
1		Autogenous blood; storage period, days							
15.5	1	42	3	247	9	3	Died, 5th day; uremia	90.0	58.0
2	1	50	3	191	63	3	Died, 6th day; blood	80.0	33.0
11.3	2	47	6	313	89	3¼	reaction		
	1	34	3	211	130	3	Died, 9th day;	111.0	61.0
3	2	30	5	319	190	3	hemothorax		
22.7	3	26	7	387	209	4½			
	4	19	9	305	92	4½			
	1	42	3	226	14	3	Died, 14th day;	72.0	53.0
4	2	37	6	347	114	3	intussusception		
14.2	3	26	8	191	100	3			
	4	31	10	309	124	3			
	5	37	13	370	186	3			
5									
10.6	1	57	3	246	64	3	Died, 3d day; blood reaction	--	--
6	1	Litter mate blood;	3	250	86	4	Died, 10th day; ascites	74.8	38.4
14.4	2	Springer spaniel	5	338	76	6	plus pleural effusions,		
	3		8	353	74	6	uremia (?)		
	1	Springer spaniel	3	275	68	5	Died, 24th day;	55.0	43.4
	2		4	152	63	4	bronchopneumonia		
7	3		5	167	45	4			
11.5	4		8	380	92	4			
	5		12	420	60	5			
	6		19	341	24	4½			
8	1	Homologous blood	3	204	86	4½	Died, 9th day;	135.9	65.4
28.0	2	of same breed;	4	155	66	4½	intussusception		
	3	Weimaraner	7	318	132	5½			
9	1	German short-haired	3	255	78	5½	Died, 5th day; internal	--	--
21.7	2	pointer	4	166	71	4½	hemorrhage (heparinization)		
10	1	Dextran	2	126	62	3	Died, 4th day;	76.9	35.4
12.0	2		3	152	59	3	intussusception		

in good health 14 days later, when it was killed for necropsy.

In the second group, which consisted of 10 dogs, a similar period of occlusion of a renal artery was combined with simultaneous nephrectomy of the right kidney and followed by repeated hemodialysis. The subsequent courses of these dogs are indicated in the Table. The changes in blood urea content and in mean arterial blood pressure related to various periods of hemodialysis are shown in Figure 1.

Hemodialysis was accomplished with apparatus of the type used by Skeggs, Leonards, and Heisler,[3] with dialyzer packs composed of six units and having a capacity of approximately 250 cc. During the procedure, the need for general anesthesia and repeated cannulation was obviated by use of dogs prepared with indwelling cannulas placed into the aorta and superior vena cava by way of the subclavian vessels.[4,5] Adverse reactions, which we have previously ascribed in dogs to the use of random homologous donor blood,[6] were avoided by using solutions of dextran, blood from litter mates, or blood from the same pure breed to fill the dialyzer packs. In five dogs, use was made of autogenous blood drawn aseptically and stored for various periods up to 57 days prior to cannulation and renal damage. Within this group, uneventful dialyses were accomplished 10 times on three dogs, with the use of autogenous blood stored for 42 days or less. Two dogs deteriorated rapidly; one died three days and one six days following dialysis with autogenous blood stored for 57 and 47 days, respectively.

The clinical course of the dogs having uremia was one of progressive deterioration in health. Initially they appeared to be more ill than the dogs subjected to bilateral

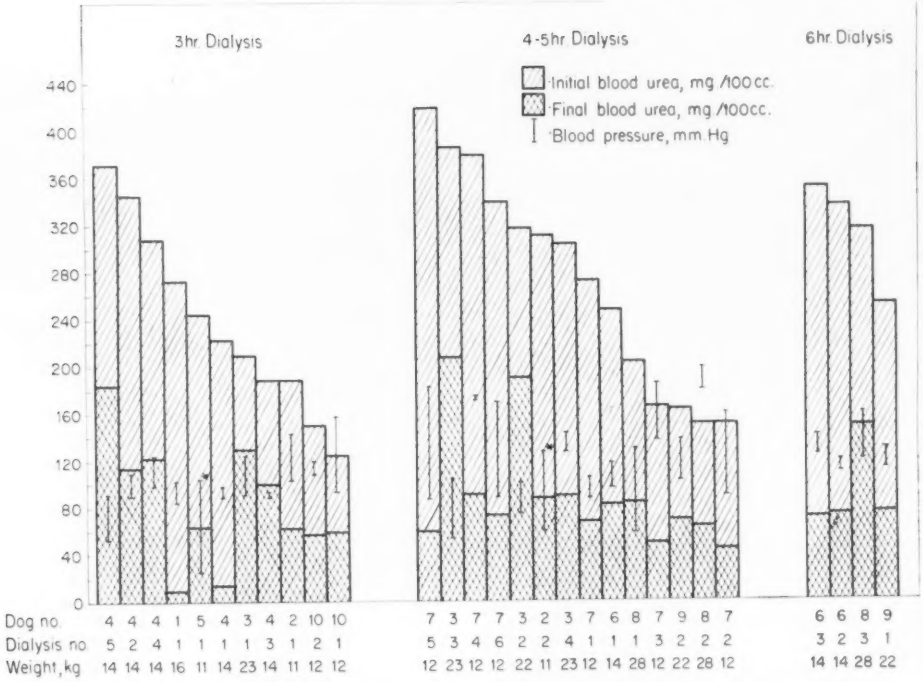

Fig. 1.—Changes in blood urea and mean arterial blood pressure during three- to six-hour dialyses.

nephrectomy, possibly because of the absorption of toxic products from the necrotic portions of the damaged kidneys. Appetite was lost early, and a marantic state was soon reached. A persistent and inexorable fall in hematocrit occurred despite the transfusion of relatively large volumes of blood, a particularly vexatious problem, owing to the limited supplies of compatible blood. Brown and his co-workers [7] noted a consistent decrease in the volume of packed erythrocytes in dogs in acute renal failure, and recent research on erythropoietic substances liberated from the kidney [8] would seem to point to their absence or suppression in the ischemic kidneys of our dogs.

Anuria usually persisted for two to three days after the insult to the kidney, but from then on a gradually increasing diuresis occurred. The specific gravity of the urine, however, at no time exceeded 1.014. All the dogs died. The dog surviving the longest lived for 24 days after renal ischemia was induced. Death of this dog was due to bilateral bronchopneumonia after six uneventful dialyses, the dialyzing pack being primed on each occasion with litter mate blood.

Causes of Death in the Uremic Dogs

The causes of death for the 10 dogs were as follows: intestinal intussusception, in 3; reaction to stored autogenous blood, in 2; manifestations of uremia, in 2; internal hemorrhage, in 2, and, as previously mentioned, bilateral bronchopneumonia, in 1.

Intestinal intussusception was the cause of death in 30% of our dogs, and occurred at the commonest situation, that is, in the ileocecal angle. Houck and associates [9] have recorded this complication in 11 of 36 bilaterally nephrectomized dogs maintained by intermittent peritoneal dialysis. Muirhead and associates [10] found intussusception in 11% of 71 nephrectomized dogs untreated or subjected to extracorporeal hemodialysis.

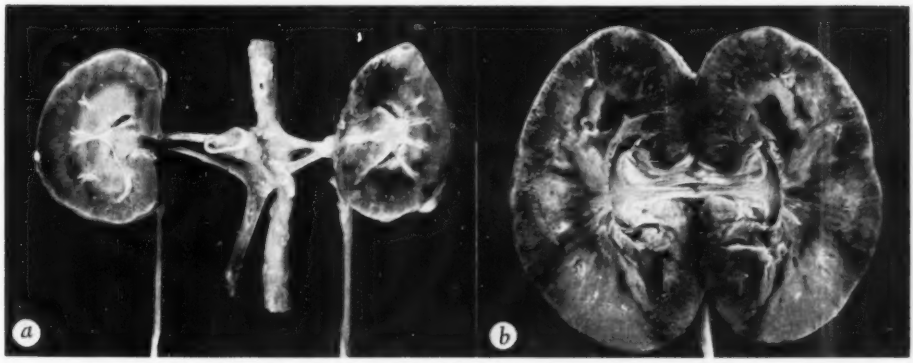

Fig. 2.—(*a*) Left renal artery occluded for four and one-half hours, 14 days previously. Note that the left kidney is smaller than the right; also note the patchy regions of infarction. (*b*) Left kidney 14 days after four and one-half hours of occlusion of the left renal artery, simultaneous removal of right kidney, and five dialyses. Note congestion of kidney.

The etiology of this condition is unknown, but at necropsy in uremic dogs that have not died of intussusception, we have noticed hypertrophy of Peyer's patches, along with marked enlargement of the ileocecal lymph nodes. Internal hemorrhage was the cause of death in two dogs. In one of them hemothorax resulted when the cannula in the subclavian artery was blown out; the other accident was thought to result directly from heparinization.

Differences in Damaged Kidneys in the Two Groups

Comparison of the two kidneys in each dog in which the right kidney had been preserved intact showed the left kidney to be small and pale (Fig. 2*a*), with patchy regions of infarction. The average weight of the left kidney in the four dogs was 17% less than that of the right. Histologically there appeared to be a loss of tubules (Fig. 3*a*). The glomeruli, which appeared to be relatively normal, were separated by cellular tissue, containing only a small number of tubules. The arcuate and interlobular arteries showed an inconsistent increase of the intimal connective tissue narrowing the lumen (Fig. 3*c*), and exhibited a homogeneous appearance of the media, with extensive fraying and reduplication of the elastic lamina. The smaller vessels demonstrated hyalinization of the media (Fig. 3*d*), with prominent proliferation of the internal connective tissue almost completely obliterating the lumen. No calcific deposits were evident.

In each dog in which the contralateral kidney had been removed at the time of the ischemic episode of the left kidney and life had been prolonged by repeated extracorporeal hemodialysis, the damaged kidney was enlarged and congested (Fig. 2*b*). At necropsy, the left kidney showed an average increase in weight of 80% over that of the right kidney when it had been removed. Microscopically, the severely damaged regions appeared in a state of coagulation necrosis. In the relatively normal regions the tubules were greatly dilated and were lined by flattened endothelium. Diminution in the actual number of tubules was not apparent (Fig. 3*b*). The arcuate and interlobular arteries were apparently normal. The smaller arteries in the necrotic regions closely resembled the corresponding vessels in the first group of dogs. In the functioning regions of the kidney the smaller arteries failed to show any abnormality. Large amounts of calcific material were present.

Comment

Efforts to prolong the lives of uremic dogs by repeated hemodialysis are seriously impeded by the lack of adequate supplies of compatible blood needed to fill the dialyzer

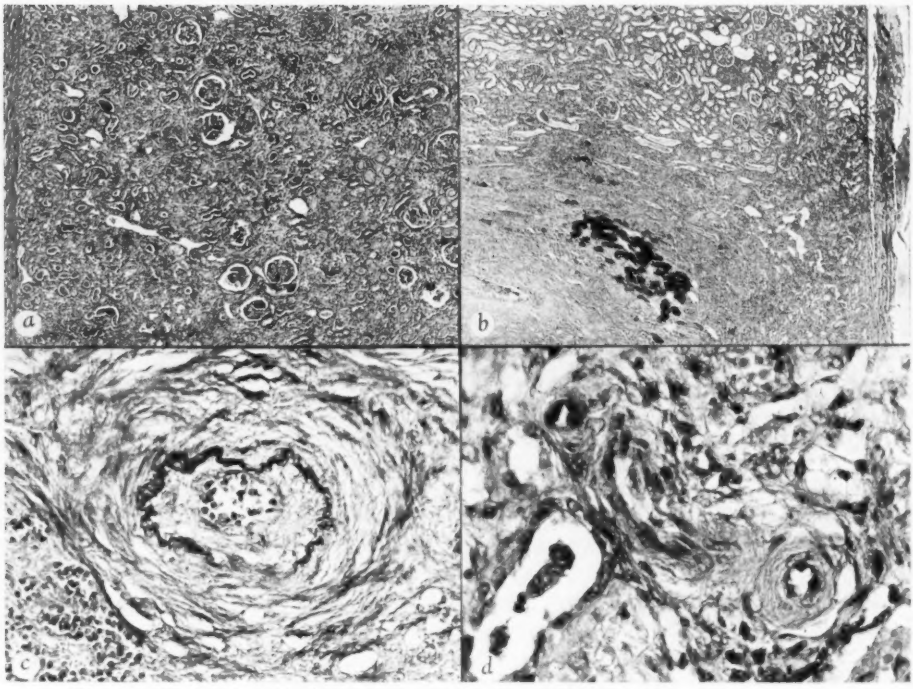

Fig. 3.—(*a*) Section of kidney demonstrating loss of tubules. Hematoxylin and eosin; reduced to 72% of mag. × 50. (*b*) Functioning region, showing dilated tubules with no apparent loss in number. Calcification at edge of infarct. Hematoxylin and eosin; reduced to 72% of mag. × 30. (*c*) Interlobular artery with marked intimal proliferation, narrowing lumen. Hematoxylin and eosin; reduced to 72% of mag. × 375. (*d*) Smaller artery cut in two planes, demonstrating hyalinization. Hematoxylin and eosin; reduced to 72% of mag × 600.

packs and to combat the anemia associated with renoprivia. Leonards and Heisler [11] reported a series of 15 bilaterally nephrectomized dogs that survived an average of 9.5 days (range, 5 to 20 days) with the aid of repeated hemodialysis. Their control group of 10 dogs not dialyzed survived an average of 6.6 days (range, 4 to 8 days).

We have been able to minimize the incidence of reactions to donor blood by the use of stored autogenous blood, litter mate or maternal blood, or blood from dogs of the same pure-bred strain (Weimaraner, German short-haired pointer). No reaction was observed when the dialyzers were filled with dextran solution instead of blood. The resulting anemia was corrected in part by the subsequent slow transfusion of washed homologous erythrocytes. Reactions which we have associated with incompatible blood were not observed in the dogs herein described.

Our finding that hemodialysis is less efficient than the retained contralateral kidney in prolonging life following four and one-half hours of occlusion of the left renal artery is probably due to four principal factors: (1) intermittency in the application of extracorporeal hemodialysis, (2) lack of adequate blood, (3) lack of renal factors, such as erythropoietin, and (4) the inherent danger of intestinal intussusception in a uremic dog.

Dogs in the hemodialysis group survived an average of 9.6 days (range, 4 to 25 days). This result agrees closely with the experiences of Leonards and Heisler [11] in bilaterally nephrectomized dogs, which apparently

did not respond adversely to homologous blood on hemodialysis. In our series, only two dogs were considered to be uremic at death. The fatal course and high morbidity in our series of 10 dogs occurred despite the apparent histologic improvement in the damaged kidney. The health of the uremic dog is difficult to maintain, and morbidity was associated mainly with a loss of appetite and weight and a progressive fall of the hematocrit. The dogs that vomited early in uremia seemed to deteriorate more rapidly. If the vomitus was foul-smelling, we suspected that intussusception of the bowel had developed in the dog; such vomitus was noted in three dogs. The procedure of hemodialysis did not seem to be injurious to the dogs in cases in which an immediate reaction to the donor blood used to fill the dialyzing pack did not occur.

Data obtained in this study suggest that in the dogs whose lives were prolonged by control of the uremia through dialysis, recovery of the damaged kidney was better than in the group of dogs in which the contralateral kidney was retained. The major factors contributing to this improvement in healing appeared to be increased circulation and vascularity. Narrowing of the lumen of the smaller arteries and loss of tubular structure, consistently noted in all four dogs whose right kidneys were preserved, were possibly indicative of a secondary or continuing circulatory embarrassment, superimposed on the original period of ischemia.

Our findings also suggest that when the clinical condition of a patient in acute renal failure justifies the use of hemodialysis, delayed application of the procedure does not jeopardize the functional recovery of the injured kidneys. At the Mayo Clinic the experience of Maher and Broadbent [12] with the artificial kidney has led them to base the application of hemodialysis on the clinical state of the patient; this is in accord with our findings.

Summary and Conclusions

An experimental study was made of the recovery of kidneys damaged by ischemia under the following circumstances: (1) conservation of contralateral kidney and (2) immediate removal of contralateral kidney followed by early and repeated extracorporeal hemodialysis. Recovery of the damaged kidney was better in the group of dogs in which the contralateral kidney was removed than in the group in which it was conserved. Impairment following removal of the contralateral kidney seemed to be due to decreased circulation, owing to narrowing of the smaller blood vessels.

Mayo Clinic.

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DISCUSSION

DR. GERSHOM J. THOMPSON, Rochester, Minn.: This paper by Dr. Edwards and associates reports only one phase of several experimental projects which have kept him busy during the 14 months he has spent at the Mayo Clinic. It was his original intention to study the problem of the experimental production of calculus disease of the kidney. In later papers he will report his experience in this field.

From this work other avenues of research developed, and, working with Dr. Grindlay, Dr. Maher, and associates, he became an invaluable member of the group which perfected techniques of using the artificial kidney.

To study properly in animals the functioning of this device, it was essential to perfect methods of damaging the kidneys. This he has done.

That many hours of labor were involved is a gross understatement. Maher and Broadbent, in a recent article on the clinical use of the Skeggs, Leonards, and Heisler artificial kidney, point out that in fact some 2000 hours of dialysis with this machine have been accomplished, during which time 240 separate dialyses have been conducted on dogs and 6 dialyses on pigs.

The device was finally used clinically 22 times in an effort to save the lives of 15 humans suffering with extreme renal insufficiency. A successful result was obtained in eight cases. These patients were subsequently discharged from the hospital, well. An additional patient recovered from acute renal failure and returned to normal renal function, but died 20 days later of pulmonary disease, unrelated to the renal problem.

Dialysis with this machine is not a simple matter. It requires a team of five or six alert persons, including a laboratory technician, who makes frequent determinations of blood constituents throughout the procedure. The dialysis as a rule lasts approximately six hours. During this time blood flow through the machine is at the rate of 200 cc. per minute. Counter to this the flow of fluid through the dialyzer pack is 800 to 1000 cc. per minute.

The details are too extensive to present here; they are available in Maher and Broadbent's report. Suffice to say that uremia is corrected through various biochemical adjustments in the plasma composition of the patient. Blood levels of urea and creatinine are reduced to at least 50% of predialysis levels. Plasma bicarbonate levels are restored to normal values when the initial values were much lower, and sodium, chloride, calcium, and potassium levels are also corrected.

This has indeed been a great contribution to the clinical armamentarium at our institution, and it has stemmed in part from Dr. Edwards' efforts in the experimental field. We humble clinicians are very grateful to him and to the other members of our staff in experimental medicine.

DR. D. EMERICK SZILAGYI, Detroit: The selection of the optimal time for the institution of hemodialysis in the oliguric patient is an important and difficult problem for the clinician. The painstaking and very difficult work that Dr. Edwards and his associates have presented suggests that the mere presence of a uremic state, even if of severe degree, is not an urgent indication for the institution of hemodialysis. It appears from their work that the presence of uremia may indeed be a stimulus for the regenerative process in the renal parenchyma. If this is so, the commencement of dialysis had best wait until the clinical state of the patient shows evidences that further delay of the relief of the uremia may be dangerous.

The decision is one of very fine clinical judgment, and so to me the most impressive lesson of this paper is that its emphasis that the most important factor in the success of using the hemodialyzer is not the technical mechanism but, rather, the judgment and experience of the clinical team.

I should like to take this opportunity to call your attention to another effect of ischemia of the kidney, which is not directly related to the problem of hemodialysis but which has both practical and theoretical importance. I shall do this very briefly.

[Slide] In a 59-year-old patient we undertook to remove an aortic aneurysm.

[Slide] In the course of the dissection, inadvertently an aberrant right renal artery was injured; in the wall of the artery an incision about

4 mm. long was repaired. The artery seemed to function well at the conclusion of the operation, two hours later.

[Slide] However, on the second postoperative day the patient began to develop marked hypertension, which became severer as time went on, in spite of a variety of hypertensive drugs administered in generous amounts.

In the meantime, congestive cardiac failure and, later, uremia of some degree developed. It became necessary to remove the kidney on the 15th postoperative day. The nephrectomy was followed by a very striking drop in blood pressure, which, after an initial temporary rise, settled to normal levels.

[Slide] This is the appearance of the removed kidney, the so-called Palomino kidney, a pale tan, swollen organ with areas of obvious necrosis. The clot, which completely occluded the right renal artery, is seen.

[Slide] The cross section of the kidney shows areas of necrosis, but there is a surprising amount of normal parenchyma.

Insofar as we have been able to ascertain, this is the only reported case of man-induced Goldblatt kidney in a human being.

DR. ERIC C. EDWARDS, Liverpool, England: I think Dr. Szilagyi has struck at the core of the matter of what I was trying to present and what I was going to state in summary, and that is this:

When should one dialyze a patient? These distorted electrolyte and plasma constituents do not seem to impair the recovery of the kidney; in fact, they may actually help it to recover.

If that is so, there is no immediate necessity to rush in to do a dialysis, and one can use one's clinical judgment and intuition, and assess exactly the time one should dialyze. One should not leave dialysis until so late that the patient's condition is bad enough to make dialysis a hazard.

Therefore, at the present time it is the practice to balance these two factors. One can delay dialysis, because uremia is not dangerous; but one must not leave dialysis until so late that the patient's clinical condition is so poor that dialysis is a hazard.

Clinical Toxicity of Antibiotics Correlated with Animal Studies

S. M. FARHAT, M.D.; D. L. SCHELHART, B.S., and M. M. MUSSELMAN, M.D., Omaha

High levels of antibiotics in the serum may be fatal.[1,2] We have found toxic levels in some patients who had depressed urinary output. These patients were on usual dosages of the antibiotics. They showed a unique pattern of signs and symptoms. They developed high fever, twitching of their extremities, lethargy, shock, and respiratory failure. These patients also had high serum levels of nonprotein nitrogen. These findings led us to determine in experimental animals what serum levels of antibiotics are toxic, whether toxic levels could cause the above signs and symptoms, and whether high levels could cause renal damage.

Material and Methods

Oxytetracycline, tetracycline,* chlortetracycline,† and chloramphenicol ‡ were studied. Each antibiotic was given intraperitoneally in three divided doses per day to a different group of rabbits. One or two animals in each group served as controls and received saline intraperitoneally. All the animals received food and fluids ad lib. The serum antibiotic level, serum nonprotein nitrogen, blood urea nitrogen, and sulfobromophthalein U. S. P. (Bromsulphalein) retention were determined in each animal before the initial injection and each day until the animal died or the experiment ended. Specimens of the liver and kidney were obtained at autopsy.

Oxytetracycline.—Oxytetracycline was given to six groups of five animals each. The first group received a daily dose of 50 mg/kg.; the second, 100 mg/kg.; the third, 150 mg/kg.; the fourth, 200 mg/kg.; the fifth, 250 mg/kg., and the sixth group 300 mg/kg. One animal in each group served as control.

Tetracycline.—Tetracycline was given to two groups. In Group 1, five animals received 250 mg/kg. of tetracycline, and one served as control. In Group 2, four animals received 300 mg/kg. of tetracycline, and one served as control.

Chlortetracycline.—Chlortetracycline was given to two groups. In Group 1, eight animals received 250 mg/kg. of chlortetracycline and two served as controls. In Group 2, four animals received 300 mg/kg. of chlortetracycline and one served as control.

Chloramphenicol.—Chloramphenicol was given in a dose of 300 mg/kg. to eight rabbits. Two animals in this group served as controls.

Results

Oxytetracycline.—Rabbits receiving a dose of 50 and 100 mg/kg. of oxytetracycline had serum levels that were only slightly elevated, none above 12.5μg/ml. The normal range of nonprotein nitrogen in rabbits was found to be 30 to 60 mg. per 100 cc. These animals showed a minimal elevation of NPN. They survived the seven-day period of the experiment.

Animals receiving 150 and 200 mg/kg. of oxytetracycline showed progressive anorexia, weight loss, lethargy, and convulsions, ending in sudden death. Diarrhea of moderate extent was noted terminally. Flaccid paralysis was noted in some of the animals.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

This project was supported in part by a grant from Chas. Pfizer & Company, Inc. From the Department of Surgery, University of Nebraska College of Medicine.

* The oxytetracycline and tetracycline for this study were supplied by Chas. Pfizer & Company, Inc. The trade name for oxytetracycline is Terramycin, and that for tetracycline is Tetracyn.

† The chlortetracycline for this study was supplied by Lederle Laboratories Division, American Cyanamid Company. The trade name for chlortetracycline is Aureomycin.

‡ The chloramphenicol for this study was supplied by Parke, Davis & Company. The trade name for chloramphenicol is Chloromycetin.

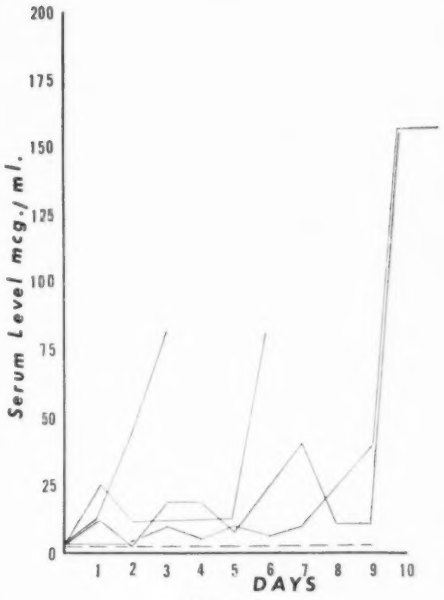

Figure 1

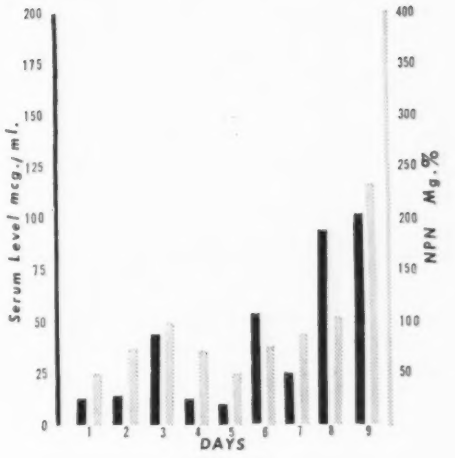

Figure 2

Fig. 1.—Serum levels of oxytetracycline in five rabbits receiving a dose of 150 mg/kg/day over a period of nine days, illustrating cumulation of oxytetracycline because of impaired renal function.

Fig. 2.—Increasing average serum levels of NPN related to increasing average serum levels of oxytetracycline over a period of nine days in the same animals as those shown in Figure 1.

Serum levels of oxytetracycline gradually rose (Fig. 1). There was no significant change in NPN until the serum oxytetracycline level reached 20μg/ml. (Fig. 2). From this stage on the rise in NPN was rapid. Death occurred with a serum level of 80μg/ml. to 160μg/ml.

Animals receiving 250 mg/kg. per day of oxytetracycline showed rapid, progressive rise in serum oxytetracycline and NPN levels. These levels were higher than those in the previous group. All animals died in two to four days with oxytetracycline levels of 160μg/ml. to 320μg/ml. They all showed evidence of anorexia, weight loss, lethargy, and diarrhea.

The group receiving 300 mg/kg. of oxytetracycline showed an identical response to that of the group receiving 250 mg/kg. of this antibiotic.

Tetracycline.—Tetracycline in 250 and 300 mg/kg. doses showed the same pattern of response as was seen with similar doses of oxytetracycline.

Chlortetracycline.—Chlortetracycline in doses of 150 and 200 mg/kg. caused progressive elevation of serum NPN and serum chlortetracycline levels. The response was similar to that after comparable doses of oxytetracycline and tetracycline. In contrast, a dose of 300 mg/kg. was extremely

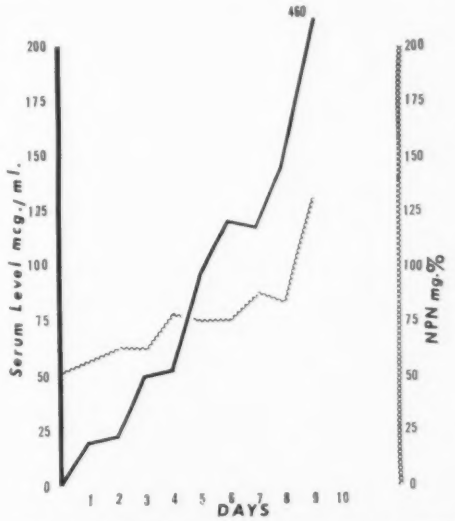

Fig. 3.—Increasing average serum levels of NPN in relation to increasing average serum levels of chloramphenicol.

toxic, and all the animals died within a period of 12 hours. Serum chlortetracycline levels as high as 320μg/ml. were found.

Chloramphenicol.—Chloramphenicol in doses of 300 mg/kg. caused slow, but progressive, elevation of the serum antibiotic and the NPN level (Fig. 3). However, in contrast to the tetracyclines, the elevation of NPN did not begin until serum antibiotic levels were as high as 40μg/ml. to 50μg/ml.

Blood Urea Nitrogen.—BUN slowly increased irrespective of the type of antibiotic used. This elevation, however, was less than that of the NPN. Sulfobromophthalein remained within the normal range throughout the experiment.

Pathologic Report

The pathologic findings were similar after all the antibiotics studied. Microscopic sections of the kidneys showed marked evidence of tubular degeneration, cellular and protein casts, and irregular crystals, resembling cystine crystals. Liver sections showed focal necrosis with a moderate degree of congestion.

Comment

It is known which doses of antibiotics are toxic because of earlier studies by other investigators. But, except for the work of Sedwitz, Bateman, and Klopp, no studies have been made to determine what the toxic serum levels are. In our study, for the tetracyclines the minimal toxic serum level was 20μg/ml. For chloramphenicol the toxic level was 40μg/ml. to 50μg/ml. At these levels the NPN begins to rise. The lethal levels ranged from 80μg/ml. to 320μg/ml., occasionally higher.

The close relationship we found between the elevation of NPN in the face of normal liver function, shown by sulfobromophthalein and tubular degeneration found microscopically, supports the belief that high serum antibiotic levels can cause renal damage. Antibiotics in general are excreted mainly by the kidneys. In the presence of renal impairment, they accumulate in the blood. The rise of serum levels to toxic levels further impairs renal function, and thus a vicious cycle is set up in which renal impairment leads to accumulation of antibiotics and this accumulation leads to further renal injury. These findings do not preclude the use of antibiotics in the presence of all forms of renal disease. For instance, we found no accumulation of antibiotics in a number of children with chronic glomerulonephritis receiving antibiotics prophylactically.

We considered the paralysis, unsteadiness, lethargy, convulsions, and respiratory failure as evidence of damage to the central nervous system, as other investigators have suggested before. The sudden respiratory failure noted in most of our animals suggests that a high serum level of antibiotics may have a direct effect on the respiratory center, perhaps by interfering in the normal function of the enzymes of the cells of the respiratory center.

Summary and Conclusions

Toxic levels of antibiotics have been found after usual doses of antibiotics in patients with decreased urinary output or impaired renal function. These patients also had a rising NPN level. In experimental animals serum levels of tetracyclines and chloramphenicol were determined after daily intraperitoneal injection of these antibiotics. Serum levels of 20μg/ml. for tetracyclines and of 40μg/ml. for chloramphenicol initiated the signs and symptoms of toxicity, as well as elevation of the NPN. Serum levels of 80μg/ml. to 320μg/ml. were found to be lethal. Serum antibiotic levels and serum NPN rose progressively and led to anorexia, weight loss, lethargy, convulsions, and respiratory failure.

Antibiotics should be used with caution in the face of renal disease. Impaired renal excretion leads to accumulation of antibi-

otics in the serum to toxic levels. Close correlation of the NPN and serum levels of tetracyclines and chloramphenicol makes the determination of NPN an excellent guide to the course of therapy with these antibiotics.

University of Nebraska College of Medicine (Dr. Musselman).

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Effect of Arginine and Glutamate on Tolerance to Intravenously Administered Ammonium Chloride

HAROLD A. HARPER, Ph.D., and JOHN Q. OWSLEY Jr., M.D., San Francisco

The intravenous administration of ammonium chloride is sometimes used in the treatment of patients with severe alkalosis. It has been suggested that the toxic reactions occasionally encountered when ammonium chloride is administered may be due to ammonia intoxication.[1-3] It is possible, therefore, that the toxicity of ammonium chloride solutions may be prevented if the increase in the blood ammonia that follows their administration can be controlled.

In various clinical states in which ammonia intoxication is a pathogenic factor, glutamic acid has been used to lower the blood ammonia.[4,5] This amino acid may lower the blood ammonia by forming glutamine, a reaction in which one mol of ammonia is utilized per mol of glutamine formed. Urea formation is quantitatively a more important metabolic route for disposal of ammonia than is glutamine formation. Urea production and a consequent lowering of the blood ammonia can be enhanced by the intravenous administration of the amino acid arginine.[6,7] The following experiments were done to compare the effectiveness of arginine and of glutamic acid in controlling the rise in blood ammonia that accompanies the intravenous administration of ammonium chloride.

Method

A solution of 0.9% ammonium chloride was administered intravenously to unanesthetized adult mongrel dogs for two hours. Blood samples were drawn immediately before the infusion was started, at 30-minute intervals during the infusion, and for 1½ hours after the infusion was discontinued. Heparin was used as the anticoagulant. The samples of blood were analyzed for ammonia nitrogen by the microdiffusion method of Conway,[8] for urea nitrogen by the method of Van Slyke and Kugel,[9] and for plasma carbon dioxide content by the method of Van Slyke and Sendroy.[10]

In preliminary tests the ammonium chloride solution was infused at various speeds to ascertain the rate that would produce a significant degree of acidosis, as well as a sustained elevation of blood ammonia. In the subsequent experiments, the effect of arginine or of glutamic acid, given as monosodium glutamate for reasons of solubility, on tolerance to intravenously administered ammonium chloride was evaluated. In the first series of experiments, a total dose of either 10 or 25 gm. of arginine or of monosodium glutamate was administered with the ammonium chloride solution that was infused. Next, the effect of the infusion of an ammonium chloride solution containing a mixture of 13 gm. of arginine and 13 gm. of monosodium glutamate was studied. In a third series of experiments, the effect of prior treatment with arginine was observed. This was done by giving approximately 12.5 gm. of arginine intravenously for one hour. During the next hour another 12.5 gm. of arginine was given together with ammonium chloride at the same rate as in the previous experiments. At the end of the second hour the administration of arginine was terminated, and the amonium chloride infusion was continued at the same rate for a third hour. The results in all of the experiments with the amino acid-ammonium chloride mixtures were compared with control data obtained in the same animal when it had been given only ammonium chloride.

Results

A two-hour infusion of ammonium chloride at a rate of 31 μEq. of nitrogen per kilogram of body weight per minute produced a rapid and steady increase of ammonia in the blood (Fig. 1). This was

From the Surgical Research Laboratories of the University of California School of Medicine.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

Supported by a grant from the National Institute for Arthritis and Metabolic Diseases (A-1053) and the Christine Breon Fund for Medical Research.

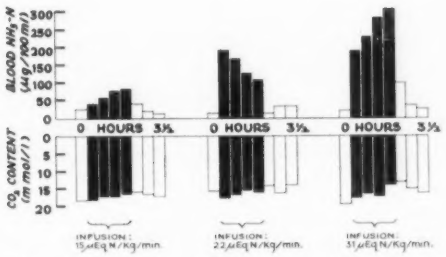

Fig. 1.—Alterations in blood ammonia and plasma carbon dioxide content during infusion of 0.9% ammonium chloride at increasing rates.

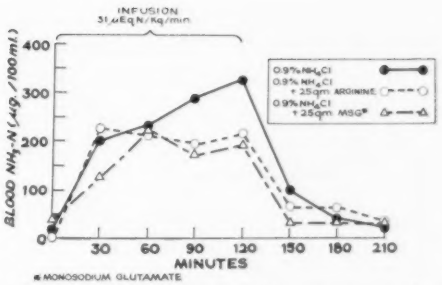

Fig. 2.—Effects of arginine or monosodium glutamate on blood ammonia during an infusion of 0.9% ammonium chloride.

associated with the development of a significant metabolic acidosis, as measured by a reduction in the plasma carbon dioxide content. Although blood ammonia levels began to decline as soon as the infusion was discontinued, the normal range was not reached for at least one hour. Infusion at lower rates produced smaller increases in blood ammonia and minimal degrees of acidosis. When ammonium chloride was given at a rate of 22μEq. of nitrogen per kilogram per minute, the initial rapid rise in blood ammonia was not sustained. This was apparently due to the ability of the tissues to remove ammonia more rapidly when stimulated by this ammonium load.

When arginine was added to a solution of ammonium chloride, which was infused at a rate of 31μEq. of nitrogen per kilogram per minute, a partial but still significant control of the blood ammonia was apparent. As shown in Figure 2, the rise in ammonia levels was slower than in the controls, and at the end of the two-hour infusion the peak level was only about two-thirds that of the control. The return to normal levels of ammonia in the blood was almost immediate, as compared with the approximately one-hour delay observed in the control.

The effects on the blood ammonia of monosodium glutamate given with ammonium chloride were similar to those observed when arginine was used, except that at 30 minutes the blood ammonia was lower with the glutamate. The intravenous infusion of glutamic acid has been reported to induce nausea and vomiting.[11,12] This also occurred in all of these experiments.

In experiments conducted with 10-gm. doses of either arginine or monosodium glutamate the increase in the blood ammonia was slightly greater after the ammonium chloride infusions than was the case when 25 gm. doses of the amino acids were used. There was no evidence of any advantage in the mixture of the two amino acids as far as control of ammonia intoxication was concerned. Prior treatment with arginine did not significantly delay the rise in blood ammonia which followed the administration of ammonium chloride, and the peak levels of ammonia in the blood were similar to those obtained when arginine was administered simultaneously with ammonium chloride.

In Figure 3, the levels of urea nitrogen in the blood after infusion of ammonium chloride alone or with arginine or mono-

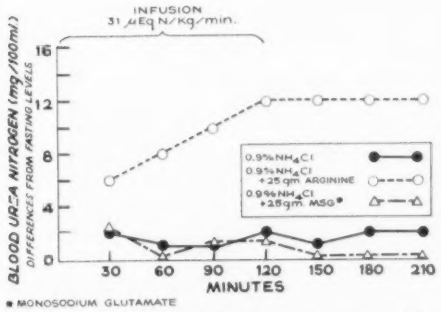

Fig. 3.—Effects of arginine or monosodium glutamate on blood urea nitrogen during an infusion of 0.9% ammonium chloride.

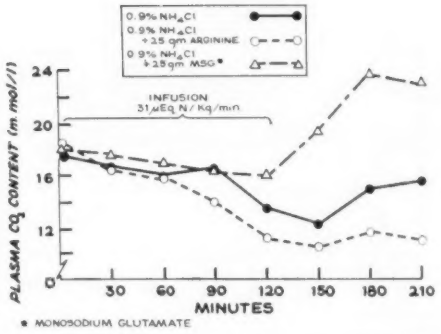

Fig. 4.—Effects of arginine or monosodium glutamate on plasma carbon dioxide content during an infusion of 0.9% ammonium chloride.

sodium glutamate are shown. The urea nitrogen levels are plotted as differences from the fasting levels. Arginine markedly enhanced urea production, in contrast to ammonium chloride alone or with monosodium glutamate.

The effects of the ammonium chloride infusions, with or without the added amino acids, on plasma carbon dioxide content are shown in Figure 4. The inclusion of arginine in the ammonium chloride solution did not affect the acidosis which was induced by the ammonium chloride alone. When monosodium glutamate was added to the ammonium chloride solution, the plasma carbon dioxide content, which declined only slightly during the infusion, increased markedly immediately after the infusion was completed.

Summary

Both arginine and monosodium glutamate exerted a significant and approximately equal effect on the control of elevations of blood ammonia which occurred after a two-hour infusion of ammonium chloride at a rate of 31μEq. of nitrogen per kilogram per minute. However, infusions of mixtures of monosodium glutamate and ammonium chloride were associated with nausea and vomiting, and, because of the necessity (for solubility) to use the sodium salt of glutamic acid, the acidifying effect of ammonium chloride was minimized. The addition of arginine to ammonium chloride solutions produced a mixture which reduced the potential toxicity of the ammonium ions and remained effective as an acidifying agent.

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Induction of Tolerance to Homografts by Nonspecific Pooled Blood

JACK A. CANNON, M.D.; PAUL I. TERASAKI, Ph.D., and WILLIAM P. LONGMIRE Jr., M.D., Los Angeles

Induced tolerance to homografts obtained by embryonic injection of the host with cells of the future donor is a phenomenon which has received extensive attention since the first report on the subject was made by Billingham and associates [1] in 1953. Until recently, such induced homograft tolerance was considered a highly individual-specific matter. In order to produce tolerance in a given individual, the evidence seemed to

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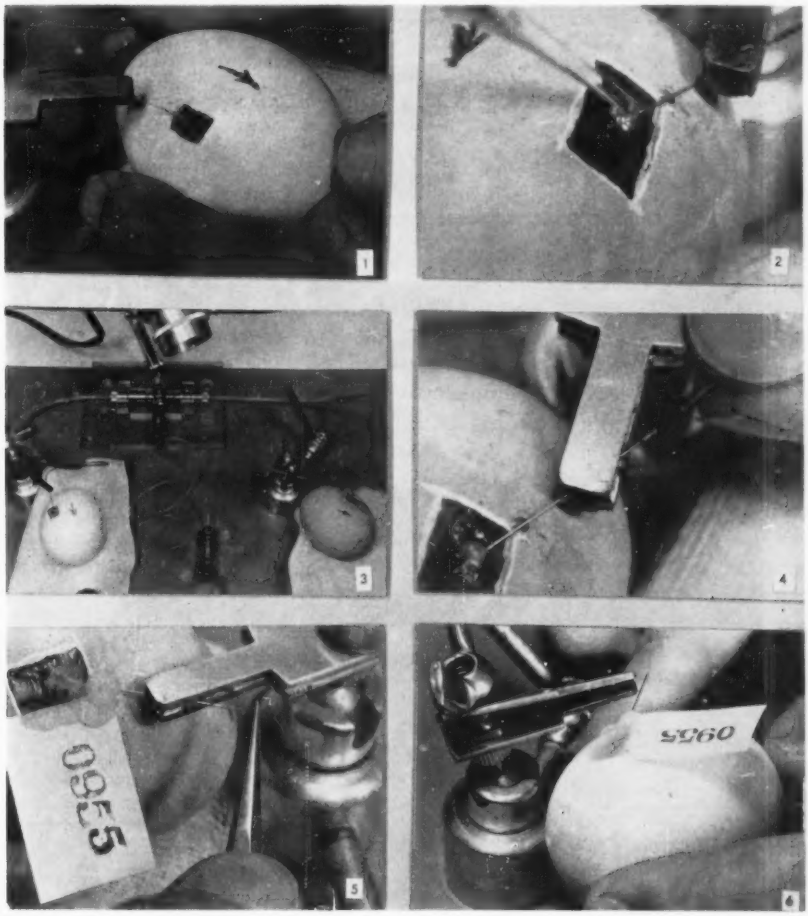
Fig. 1.—Steps in the technique of embryonic venipuncture and cross transfusion in the 10- to 16-day incubated chick embryo.



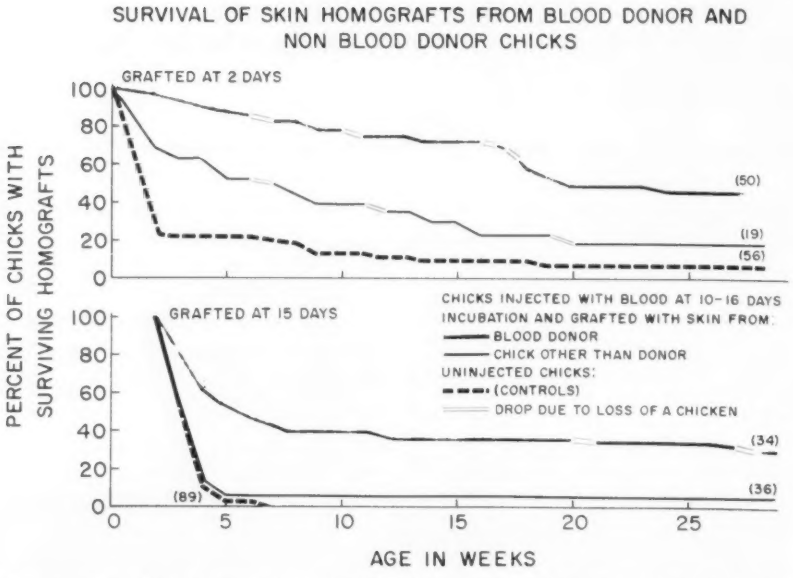


Fig. 2.—The effect of non-individual-specific induction of tolerance by host infusion with blood from a donor other than, but of the same breed as, the future skin donor.

indicate that living cells from the individual future donor must be injected into the individual future host during the embryonic period of the host. Our recent studies of the homograft problem have dealt with induced tolerance in the chick. The technique of inducing tolerance between 10- to 16-day-old, incubated chick embryos has been described elsewhere[2] (Fig. 1). The presence or absence of tolerance is tested by interchanging skin homografts between 1-day-old or 14-day-old chicks; this technique has also been described elsewhere.[3]

Some of our most recent work[4] has demonstrated not only that tolerance can be induced between two unrelated chicks of different breeds by interchange of blood between the two but also that a definite degree of tolerance is obtained if skin from a chick of the same breed as the blood donor but other than the donor is applied as a test graft to the treated host. The incidence of this non-individual-specific tolerance is not as high as when the interchange of blood *and* skin is maintained between individuals, but it occurs in a highly significant incidence (Fig. 2).

It was the purpose of the present work to test the effect of using pooled blood from several individuals of one breed to induce tolerance in an individual of another breed and then test the treated individual for tolerance to skin from other individuals of the blood-donor breed.

Methods

Blood Pooled from Four to Eight Embryos.—In this experiment, 0.4-0.6 ml. of blood was taken from each of four to eight 14- to 16-day incubated White Leghorn (WL) chick embryos, mixed with 0.05 to 0.1 ml. of heparin solution (1000 U. S. P. units/cc.), and pooled in a single test tube. In turn, 0.4-0.6 ml. of blood was withdrawn from New Hampshire (NH) embryos of a corresponding age, and then each received an equal amount of the thoroughly mixed, pooled WL blood. Likewise, the withdrawn NH blood was pooled and injected into WL embryos. In this manner, the blood withdrawn from each group of blood recipients formed the pool for the next group. With such a scheme, 70 hatched, and 51 were alive and healthy after two weeks. The hatched chicks received a skin graft from a bird which was not a donor to the blood pool but which was of the blood-donor breed. Twenty-two of the newly hatched chicks were grafted at 2 days with skin from a 2-day-old donor, while 29 were grafted at 15 days from 15-day-old

skin donors. On the basis of rough counts, each embryo received an average of 1,100,000,000 blood cells.

Blood Pooled from Twenty-Six Embryos.—An average of 0.1 cc. of blood was taken from each of 26 WL embryos, incubated for 14 to 16 days. The blood was pooled by drawing it directly into a polyethylene tube containing 0.02 cc. of heparin solution (1000 U. S. P. units/cc.) and emptying it into a Lusteroid centrifuge tube after withdrawal from each embryo. After being centrifuged for 30 minutes, the serum was drawn off, and the cellular layer was resuspended with a small amount of saline. Blood from 26 NH embryos was also obtained and treated in similar fashion. Fifty-four embryos, incubated for 14 to 16 days, were then injected with a portion of the pooled blood cellular suspension, which contained, on an average, 350,000,000 blood cells from the blood pool taken from the breed opposite that of the recipient. Of the 54 embryos, only 30 were alive two weeks after hatching, the time selected for grafting in this experiment. The 30 chicks were grafted at 15 days after hatching with skin from one-day-old chicks of the breed opposite that of the host. Grafts were then read at weekly intervals and the results plotted against the results in a like number of untreated, but similarly grafted, controls.

Results

Blood from Four to Eight Embryos.—The 22 treated chicks which were grafted at two days of age showed a 97% take of homografts at four weeks after grafting, as compared with only a 20% take in the controls. At 15 weeks after grafting, the persistent take in the treated chicks had dropped to 36%, as compared with 9% for the untreated controls. At 25 weeks the persistent take in the treated chicks had dropped to 16%, as compared with 8% in the untreated controls.

Of the 29 treated chicks grafted when 15 days of age with 15-day-old skin, 56% showed surviving homografts four weeks after grafting, whereas all the homografts in the control chicks had sloughed. At 25 weeks of age, or 23 weeks after grafting,

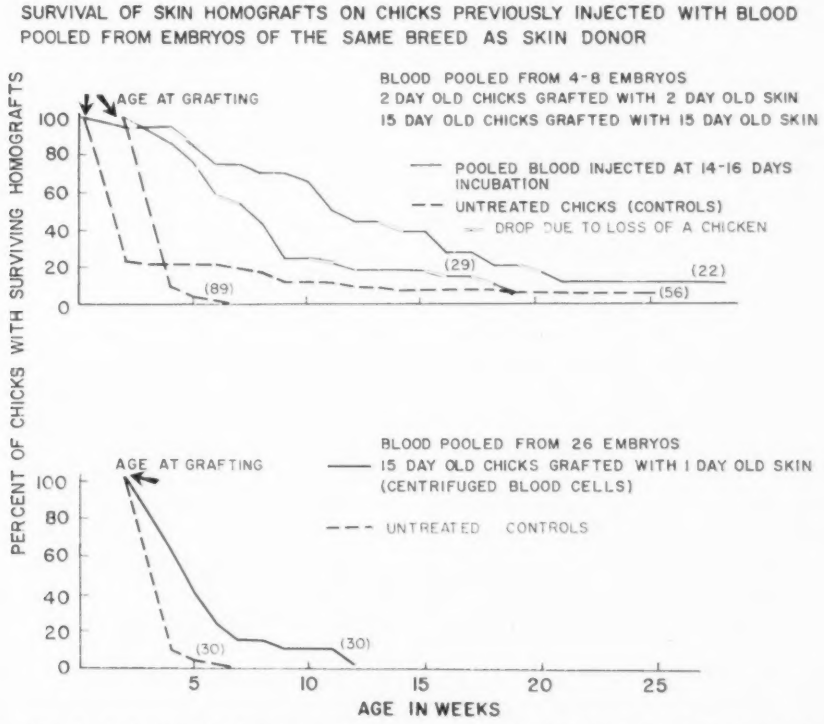

SURVIVAL OF SKIN HOMOGRAFTS ON CHICKS PREVIOUSLY INJECTED WITH BLOOD POOLED FROM EMBRYOS OF THE SAME BREED AS SKIN DONOR
PERCENT OF CHICKS WITH SURVIVING HOMOGRAFTS
AGE AT GRAFTING
BLOOD POOLED FROM 4-8 EMBRYOS
2 DAY OLD CHICKS GRAFTED WITH 2 DAY OLD SKIN
15 DAY OLD CHICKS GRAFTED WITH 15 DAY OLD SKIN
POOLED BLOOD INJECTED AT 14-16 DAYS INCUBATION
UNTREATED CHICKS (CONTROLS)
DROP DUE TO LOSS OF A CHICKEN
(89)
(29)
(22)
(56)
BLOOD POOLED FROM 26 EMBRYOS
15 DAY OLD CHICKS GRAFTED WITH 1 DAY OLD SKIN (CENTRIFUGED BLOOD CELLS)
UNTREATED CONTROLS
(30)
(30)
AGE IN WEEKS

Fig. 3.—Induction of tolerance to skin homograft in the chick by intraembryonic injection of pooled blood.

there was a persistent 8% of viable homografts in all the surviving chicks.

Blood from Twenty-Six Embryos.—Results from grafting the 30 treated chicks with one-day-old skin did not show such a striking difference from those for the untreated controls. At four weeks after grafting, 17% of the treated chicks showed surviving homografts, and all of the grafts on the untreated controls had sloughed. However, by 10 weeks after grafting all of the homografts on the treated chicks had also sloughed.

Comment

It can be seen by comparing the graphs in Figures 2 and 3 that pooled blood from four to eight embryos is essentially as effective in inducing a degree of non-individual-specific tolerance as is blood from one embryo. Unfortunately, we find that, on close analysis of the conditions of the experiment in which blood pooled from 26 embryos was used, the poorer results may well be explained on the basis (1) that the blood was centrifuged and (2) that a smaller total number of cells was injected than in the comparable group grafted also at 15 days of age but with blood from 4 to 8 embryos. Nevertheless, it would seem that these experiments do show that, under the conditions imposed, induced tolerance is far from entirely individual-specific. A higher incidence of tolerance is, of course, obtained when blood and skin come from the same donor (Fig. 2), but the requirement is not absolute.

The existence of a genetic relationship between host and donor strains is not a factor here, since in no instance have we observed a persistent take of a skin homograft in chicks of the strains used, whether the grafts were tested by interstrain or intrastrain homografting and when grafts were applied between chicks 14 days of age or older.

We feel it is doubtful that results such as these could have any direct clinical application. Nevertheless, some further understanding of the basic homograft reaction and its mechanism is permitted. It would appear to us that these results indicate that the factors which control the ultimate crystallization of complete individual specificity in the adult are not completely developed or unalterable in the embryo and infant. Their final characteristics undoubtedly are under the precise control of hereditary factors in the genes and chromosomes, provided no tampering with the normal developmental mechanism occurs. However, it would appear that, at least in the chick embryo, alterations in the mechanism responsible for individual tissue specificity of the individual are possible. How much adaptation of the homograft to the host is a factor here in the eventual long-term survival of a given homograft cannot be evaluated under the conditions of the experiment. Nevertheless, some of our other work [5] indicated to us that the tissue specificity of infant chick skin is also alterable to a degree. Consequently, we feel that the main significance of work of this type is to add some credence to the concept that the homograft reaction is alterable and, with advancing knowledge, may be understood someday well enough to permit clinical use of homovital tissue grafts.

Summary

The induced tolerance in chicks to 2- and 15-day-old skin homografts placed on 2- and 15-day-old hosts treated by intraembryonic injection of blood cells from donors of the same breed as the skin donors but different individuals. Pooled blood injections from four to eight donors were found to be as effective as blood from a single donor of the same breed but from an individual other than the skin donor. The tolerance induced is not as great as that obtained when blood and skin come from the same donor, but the non-individual-specific induction of homograft tolerance is nevertheless definite and is contrary to the evidence and opinion of the past. Use of blood pooled from 26 embryos was found to be less effective and in no instance permanent in producing tolerance to a skin

homograft, but dosage factors rather than the number of donors to the pool may have been an important factor here.

The significance of this evidence is discussed with relation to the homograft problem. No immediate clinical application is foreseen.

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Transposition of Portal Vein and Inferior Vena Cava in Dogs with Experimental Cirrhosis of the Liver

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The definitive surgical treatment of portal hypertension secondary to cirrhosis of the liver is intended to lower portal venous pressure and thus prevent hemorrhage from collateral venous channels, usually esophageal varices. Various clinically successful procedures have been developed to shunt the portal blood around the obstructing hepatic vascular bed.[1] A disadvantage of the shunting procedures currently in use is the deleterious effect on hepatic function that may follow a reduction in blood supply to the liver. This has been demonstrated experimentally in dogs with Eck fistulas.[2,3] Deterioration of hepatic function has also been observed in some patients following portacaval shunt.[4,5] By some authors it has been considered problematical whether this hepatic dysfunction might be due to diminution in the total blood supply or simply to diversion of the portal blood.

Silen et al.[6] have shown that dogs with a surgical transposition of the portal vein and vena cava maintained a comparatively normal liver function, in contrast to dogs with Eck fistulas. Their studies made it appear likely that maintenance of an adequate blood flow to the liver was a major factor in preservation of hepatic function. In order to try to apply this information to the clinical treatment of patients with portal hypertension, it seemed desirable to investigate whether liver function was as well maintained when caval blood was shunted into an obstructed hepatic venous system. For this purpose the following experiments were done.

From the Surgical Research Laboratories of the University of California School of Medicine.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

Supported by a grant from the National Institute for Arthritis and Metabolic Diseases (A-1053) and the Christine Breon Fund for Medical Research.

Experimental Study

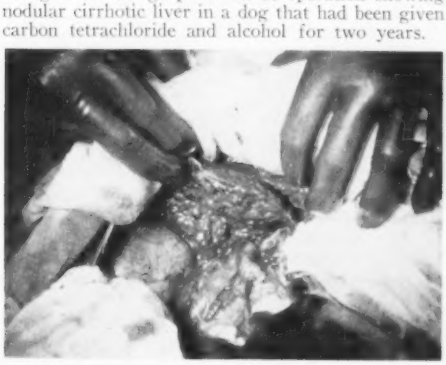
Twenty-one dogs were selected for these experiments. They were treated with carbon tetrachloride and alcohol for periods up to two years in an attempt to produce cirrhosis of the liver. Ten animals survived prolonged treatment with the carbon tetrachloride and alcohol mixture, but only four developed portal hypertension and were therefore considered suitable for studying the effect of portacaval transposition. The alterations in hepatic structure induced by carbon tetrachloride and alcohol were studied histologically to evaluate the degree of parenchymal damage and subsequent cirrhosis. Hepatic damage was estimated on the basis of necrosis or hydropic degeneration of parenchymal liver cells. The degree of cirrhosis was judged on the basis of altered reconstruction of liver, parenchymal fibrous proliferation, collagen deposition, and altered vascularity. The cirrhosis was classified as slight, moderate, marked, and severe. Portal venous pressure was considered significantly elevated if above 15 cm. of water.

Various chemical studies indicative of liver function were performed preoperatively on the cirrhotic animals selected for portacaval transposition. The total protein of the serum ranged from 6.5 to 8 gm. per 100 ml., with serum albumin levels from 0.9 to 3.2 gm. per 100 ml. All of the dogs had slight to moderate depression of sulfobromophthalein (Bromsulphalein) clearance.

Serum bilirubin, blood urea nitrogen, and hematocrit were all in the normal ranges. Blood ammonia levels varied from 24μg. to 105μg. per 100 ml. The decrease in the serum albumin correlated most closely with the degree of severity of the liver cirrhosis and appeared to be the best chemical index of the progression of liver damage.

The four cirrhotic dogs with abnormally increased portal venous pressures were examined through right subcostal abdominal surgical incision; open-drop ether anesthesia was used, and aseptic precautions were observed. Portal pressure determinations were made by needle puncture directly into the portal vein. The portal venous pressures were found to vary from 27 to 33 cm. of water. All of the dogs had grossly nodular levers (Fig. 1). In three of the animals the nodules varied in size from 3 mm. to 2 cm., and in the fourth there were fine nodules, ranging from 2 mm. to 1 cm. in size, uniformly distributed throughout the substance of all the livers. Biopsy specimens of representative portions of each liver were taken. The histological appearance in each case was that of periportal fibrosis with coarse regenerative nodule formation (Fig. 2*A* and *B*). Histologically the liver cirrhosis found at operation in these animals was graded as severe in two, marked in one, and moderate in the other. Although none of the animals had evidence of ascites preoperatively, in each case straw-colored fluid was seen in the peritoneal cavity.

Fig. 1.—Photograph taken at operation showing nodular cirrhotic liver in a dog that had been given carbon tetrachloride and alcohol for two years.



Portacaval transposition was performed in the four animals with cirrhosis and portal hypertension, and all tributaries of the portal veins were divided and ligated above the site of transposition (Figs. 3 and 4). In some cases it was necessary to ligate the right lumboadrenal vein to facilitate mobilization of the inferior vena cava. Vascular anastomoses were performed with 0000 braided silk in a continuous over-and-over suture. In one animal technical difficulties made it necessary to insert a crimped nylon vascular prosthesis 2 cm. in length to bridge a gap between the inferior vena cava and the proximal part of the portal vein entering the liver. Pressures in the shunted portal system ranged from 4 to 8 cm. of water. Pressures in the caval system measured at the femoral vein during the postoperative period ranged from 19 to 27 cm. of water.

All of the animals received intravenous fluids and transfusions of whole blood as required during and after the operation, and 300,000 units of penicillin was administered daily to each dog for seven days after operation.

These four animals have subsequently been observed for four to six months postoperatively. Early in the postoperative period it became apparent that two of them were showing signs of increasing lassitude and progressive loss of weight. Signs of ammonia intoxication were also observed, and this was confirmed by measurement of the blood ammonia, which was found to be significantly increased over the preoperative level. They were treated with arginine solutions administered intravenously [7,8] and with neomycin orally,[9] and by these measures ammonia intoxication was successfully controlled. However, because of the recurrent episodes of ammonia intoxication occurring in these two dogs, it has been necessary to repeat this regimen of therapy with arginine and neomycin several times. More recently the symptoms of ammonia toxicity have been ameliorated by a reduction of protein in the diet, together with the occasional administration of neomycin; even so, their blood am-

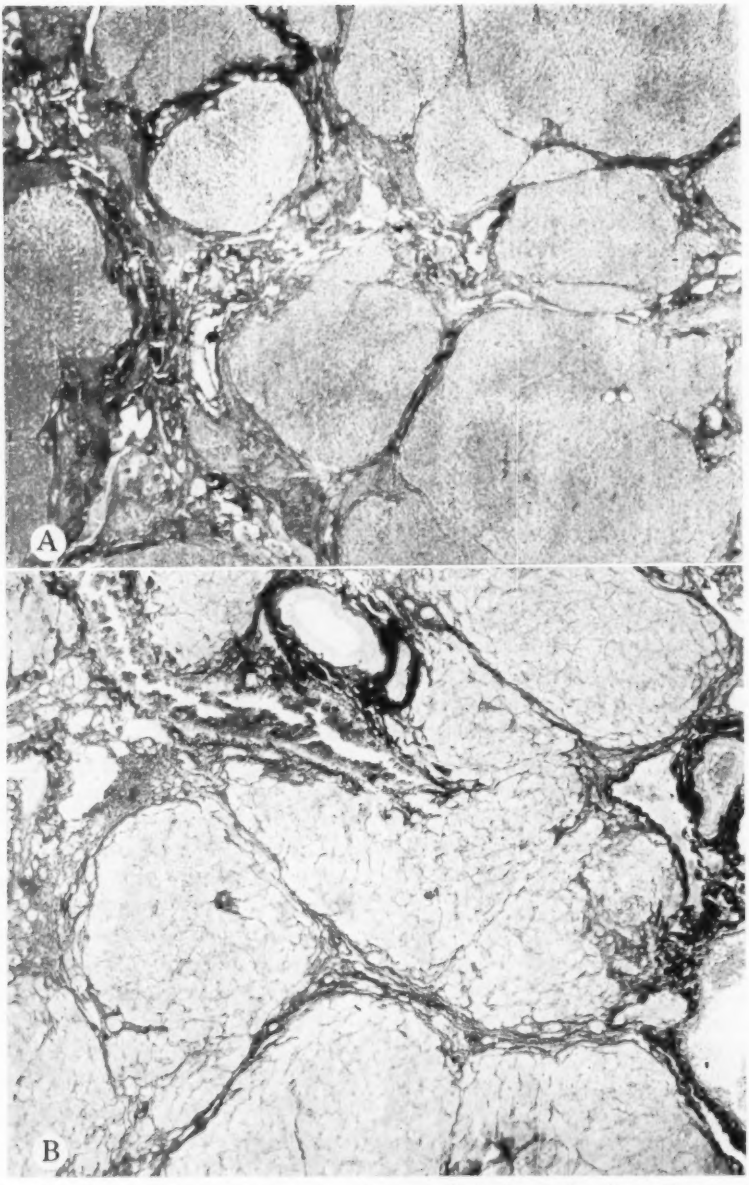


Fig. 2.—*A*, photomicrograph showing advanced cirrhosis of the liver. The extensive fibrosis has markedly segmented the parenchyma and disrupted the normal vascular relationships. Regenerative nodule formation further complicates the morphologic alteration. *B*, photomicrograph of moderately advanced cirrhosis of the liver. There are irregular nodular degeneration of the parenchymal cells, fibrous septation of the parenchyma, and increased angiogenesis.

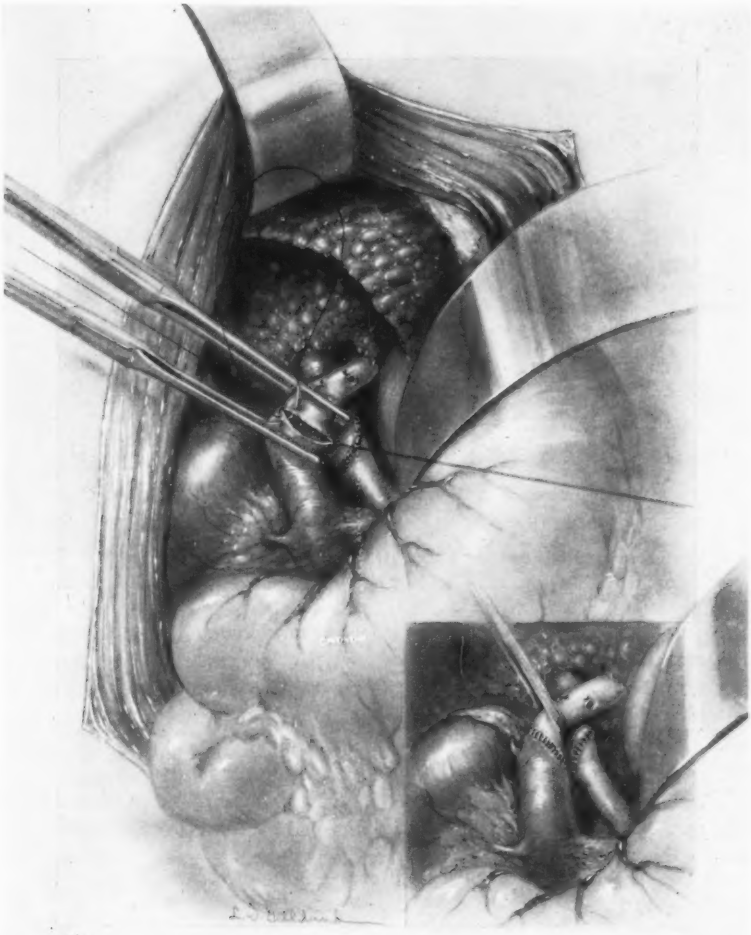


Fig. 3.—Drawing made at operation showing technique of transposing the inferior vena cava and the portal vein in a cirrhotic dog.

monia remains above normal. It was suspected that this could be accounted for by the occurrence of thrombosis of the anastomosis between the distal vena cava and the proximal portal vein in these two dogs, which would convert them into animals with Eck fistulas. It was possible to prove that this was so in one case by means of x-ray venograms (Fig. 5).

After approximately six months of observation, certain metabolic trends were apparent in the experimental animals. Ammonia intoxication did not occur in the two cirrhotic dogs in which portacaval transposition was done and in which both anastomoses had apparently remained patent; the clearance of sulfobromophthalein (Bromsulphalein) was either unchanged or slightly below that of the preoperative level. In the two dogs with presumed thrombosis of the anastomosis between the inferior vena cava and the proximal portal vein, a decline in sulfobromophthalein clearance was definitely evident, and there were also a

Figure 4

Fig. 4.—Photograph taken after portacaval transposition had been performed in a dog with cirrhosis. The retractor indicates the inferior vena cava after anastomosis to the proximal portal vein.

Figure 5

Fig. 5.—X-ray venogram showing obstruction of the anastomosis between the inferior vena cava and the proximal portal vein. Note collateral venous channels.

progressive loss of weight, anemia, a decrease in serum albumin, and marked intolerance to ammonia. In contrast, the two dogs with apparently functioning portacaval transposition gained weight and were not anemic. Their serum albumin remained stable or increased slightly as compared with preoperative levels, and there was no evidence of intolerance to ammonia.

Summary

1. Cirrhosis of the liver was produced in dogs by oral administration of mixtures of carbon tetrachloride and alcohol.

2. In four dogs with gross and histological evidence of cirrhosis and associated portal hypertension, surgical transposition of the portal vein and vena cava was performed.

3. These four animals were subsequently observed for periods of four to six months following portacaval transposition. Two apparently developed thrombosis of the anastomosis between the distal vena cava and the proximal portal vein. In these two animals recurrent episodes of ammonia intoxication occurred. There were also decreased clearance of sulfobromophthalein (Bromsulphalein), progressive loss of weight, anemia, and hypalbuminemia. In contrast, the two cirrhotic dogs with functioning portacaval transpositions gained weight and were not anemic. The clearance of sulfobromophthalein and the levels of serum albumin remained stable, and there was no evidence of intolerance to ammonia.

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DISCUSSION

DR. JAMES S. CLARKE, Los Angeles: Dr. Owsley and his associates have extended previous studies from the same laboratory on the effects of Eck fistula and portacaval transposition on liver functions of normal dogs (Silen, W., et al.: A. M. A. ARCH. SURG. 74:964, 1957). With Eck fistula liver functions became progressively impaired, whereas they were mostly unaltered following transposition. The present work, carrying observations to dogs with cirrhotic livers, is an important further step toward the clinical problem of finding a shunting operation which can lower portal pressure and still maintain a good blood flow to the cirrhotic liver, avoiding so far as possible the liver damage that follows formation of an Eck fistula.

The oral ammonia tolerance test is an understandable exception to the general rule that portacaval transposition does not impair liver function. The ammonia is presented by the portal venous blood to the liver for extraction, and with transposition this blood by-passes the liver at first. An analogous situation may exist with regard to a humoral substance we have been studying. We have measured the effect of portacaval transposition on the 24-hour output of HCl from Heidenhain pouches of dogs with normal livers. Each of seven dogs showed a profound increase in acid secretion ranging from 87% to 850% (mean, 410%) after transposition. We interpret this highly significant increase ($P<0.001$) as due to the increased effect, after shunting of portal blood around the liver, of a humoral secretagogue which originates in the abdominal viscera and is normally inactivated in the liver. These findings may explain the increased incidence of ulcer in patients with cirrhosis and the occasional development of new ulcers in patients soon after portacaval shunt.

Continued careful studies of the type Dr. Owsley has shown us here, utilizing animals with cirrhotic livers, will be required to obtain a firm answer as to which shunting procedure will best correct portal hypertension and still preserve liver function.

DR. HENRY SWAN, Denver: I would like to congratulate Dr. Owsley on his second very nice presentation this morning.

My discussion is really in the form of a question. My colleague, Dr. Eiseman, found that in normal dogs a total transposition between the portal system and the venous system was poorly tolerated unless supported by postoperative corticosteroids. A large percentage of animals without this treatment died in a shock-like state in the postoperative period.

It is to be remembered that in this preparation the blood from both adrenal veins will go directly to the liver, and the action of the liver in conjugating the active hormones is well known. If, however, the adrenal veins in these animals are ligated, the outflow from the adrenal glands will be by way of the lumboadrenal veins into the collateral circulation of the retroperitoneal area, and will thus avoid going to the liver. If this step is taken, the animal will survive.

If I saw and interpreted the first slide of Dr. Owsley's correctly, I noticed a tie around the right adrenal vein. Perhaps Dr. Owsley did this deliberately to avoid this complication. On the other hand, Dr. Owsley's animals were cirrhotic.

I should like to ask whether Dr. Owsley would comment on the thought that, since his animals were cirrhotic, their livers were sufficiently damaged that they did not deactivate the corticosteroids, and thus allowed survival of the animals, or whether he deliberately ligated the adrenal veins.

DR. JOHN HARPER GRINDLAY, Rochester, Minn.: I would like to congratulate Dr. Owsley and Dr. McCorkle and their associates. I hope very much that they will continue to work in this field of research. We, too, have been working in it. At present Dr. Adson, along with Dr. Hallenbeck, Dr. Bollman, and I, are working along the same lines as Dr. Owsley.

I shall not answer Dr. Swan's question, but I can guess what Dr. Owsley's answer will be—that there is no appreciable mortality for transposition of the abdominal vena cava and portal vein if the aorta is occluded above the diaphragm during the procedure of anastomosis.

I would now like to throw some mud in the water just to make this subject even more confusing. We have found that when an Eck fistula is performed on a normal dog, invariably the symptoms of Eck fistula occur. However, if the fistula is performed on a dog that previously has had obstruction in the portal system or cirrhosis, then the Eck fistula symptoms do not occur.

I would like to ask Dr. Owsley whether he continued the toxic stimulus which produces the cirrhosis. In his animals he said carbon tetrachloride

and alcohol were given over a two-year period. Did he continue to administer the carbon tetrachloride and alcohol after the shunt was performed on these four dogs, or just on the two dogs that had no difficulty after the procedure?

It is known that the dog will go into a normal state after a toxic cirrhosis stimulus is removed; that is, the dog will recover, and a couple of years later these nodules on his liver will disappear and he will look like a rather normal dog. The fact that these two dogs have done so well may not be an indication that the shunt or transposition has had anything to do with it unless the cirrhosis stimulus was continued.

DR. JOHN Q. OWSLEY JR., San Francisco: Dr. Clarke told me, in a discussion yesterday, that it had recently been reported at the meeting of the Clinical Congress in Atlantic City that some workers in St. Louis had described increases in the secretion from Heidenhain pouches in dogs with simple Eck fistulas similar to those he reports in dogs with portacaval transposition; and so it may be more related to the shunt per se than to the transposition.

In answer to Dr. Swan's question: In three of the cirrhotic dogs it was necessary to tie and divide the right adrenal vein to facilitate mobilization of the inferior vena cava, and in the fourth animal the vein was left intact. In doing transpositions in normal dogs, we found that it makes no apparent difference in their recovery postoperatively whether the vein has been ligated or has been left intact.

Dr. Grindlay mentioned occlusion of the aorta. We have had no experience with this technique and so have no answer to his question.

We have not treated the dogs with carbon tetrachloride since their operations, but Dr. Crane, our pathologist, feels that from an examination of the liver it seems quite unlikely, with the considerable amount of fibrous tissue deposition, that these dogs will ever return to a normal status.

Observations on the Hemodynamic Effects of Experimental Internal Mammary Artery Ligation

RODMAN E. TABER, M.D., Detroit, and THOMAS MARCHIORO, M.D., Denver

Although the surgical treatment of congenital and rheumatic heart disease has undergone remarkable expansion and refinement during the past 12 years, progress in the surgical therapy of arteriosclerotic heart disease has remained relatively stationary. The employment of at least 15 different surgical procedures for the treatment of this condition bears witness to the inconclusive results.[1-9]

This presentation concerns an attempt to study basic hemodynamic principles as they apply to experimental internal mammary artery ligation. Experimental methods were developed to gain information concerning the pressure and flow relationships in the internal mammary-pericardiophrenic artery system which would demonstrate whether the surgical procedure under investigation could logically be expected to increase blood flow through the desired channels. The existence of these channels has been known for many years and has been confirmed by injection studies.[8] Only recently has an attempt been made to utilize them as collateral routes for the purpose of increasing the flow of arterial blood to the ischemic myocardium.[8]

Methods

Mathematical formulae pertaining to liquid flow through small tubes are only crudely applicable to a clinical problem such as the one under investigation. These formulae are basically derived from Poiseuille's law, which states: $\frac{V}{t}=\frac{\pi P\Delta 4}{8ln}$, where $\frac{V}{t}$ represents volume flow per unit time; $P\Delta$ represents pressure differential; l represents the length of tubing under consideration, and n, the factor of viscosity. Inasmuch as this basic formulation and its many modifications pertain to rigid tubes with fixed resistance and laminar flow, they cannot be strictly applied to the vascular system of a biologic experiment. Therefore, one must be content with the basic relationships represented by

$$F \text{ (flow) is equivalent to } \frac{P \text{ (pressure)}}{R \text{ (resistance)}}.$$

I. The first series of experiments consist of pressure measurements in the subclavian artery performed before and after ligation of the internal mammary arteries. A polyethylene catheter was introduced into the subclavian arteries of mongrel dogs weighing between 10 and 20 kg. Anesthesia was maintained with ether, and manipulations of the internal mammary arteries were carried out through a thoracotomy in the left lateral fourth interspace. Both vessels were subsequently clamped through this incision. The tip of the catheter was passed to the region of the internal mammary artery orifice on the left side. Pressure measurements were made when the depth of anesthesia and the arterial pressure were stable.

II. Owing to the small size of the dog's pericardiophrenic artery, it was found difficult, if not impossible, to measure blood flow or pressure in this vessel with available techniques. Therefore, in order to gain information concerning flow and pressure in the pericardiophrenic artery, this portion of the arterial system was partially reduplicated using plastic tubing of appropriate sizes (Fig. 1). The aorta, subclavian and branchial arteries, and internal mammary and pericardiophrenic arteries were represented by lengths of vinyl tubing connected to a water reservoir. Pulsatile flow was obtained through use of a Sigmamotor pump. The "aortic" flow was established as a base line at 4 liters per minute, and the flow through the various branches was adjusted to proportionate amounts by partially occluding clamps at the tubing ends. This adjustment also produced pressure levels in the various branches which were proportionate to the pressure in the aorta. Pressures were determined by the use of aneroid manometers. Flow was measured as free flow from the tubing. A series of flow determinations was made at each of several resistance (and therefore pressure) settings.

Thoracic Surgical Division, Henry Ford Hospital (Dr. Taber).

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

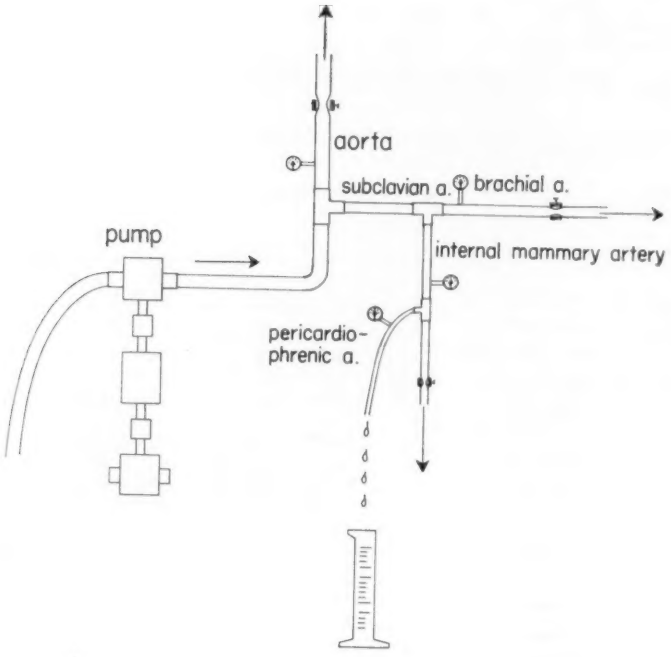

Fig. 1.—Diagrammatic representation of the pericardiophrenic-internal mammary artery system constructed of plastic tubing.

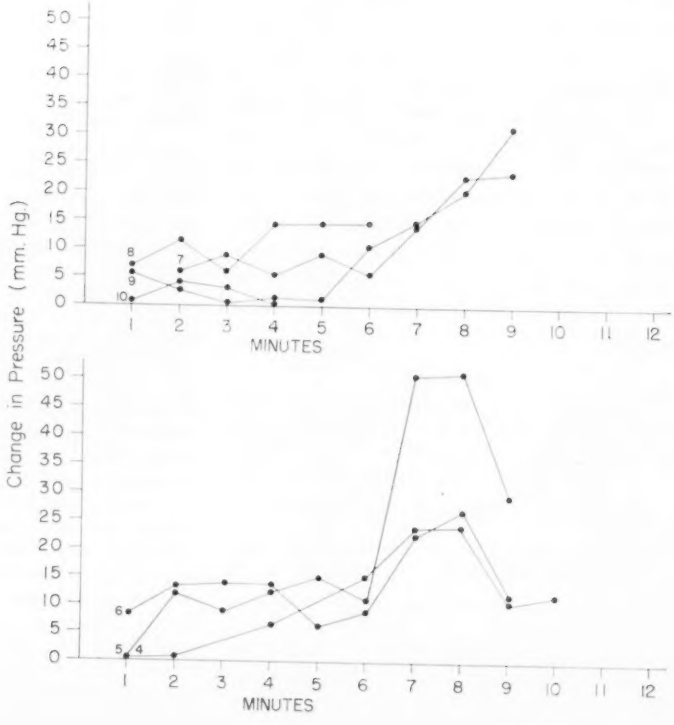

Fig. 2.—Alterations in subclavian artery pressure produced by internal mammary artery clamping.

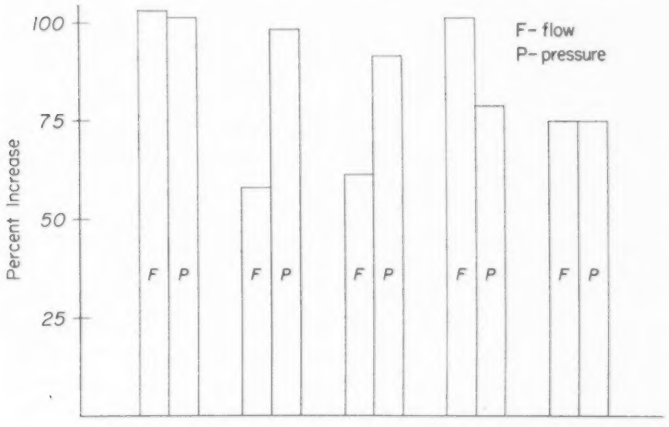

Fig. 3.—"Pericardiophrenic artery" flow and pressure changes produced by "internal mammary artery" clamping (plastic-tubing system). Five representative determinations are shown. A 50% to 100% increase in flow and pressure over basal levels was consistently observed.

Results

I. In this portion of the investigation, 7 of 10 preparations were considered as suitable for analysis. In six of the seven experiments, there was a pressure elevation in the subclavian artery of 6 to 50 mm. Hg, which was sustained throughout the period of internal mammary artery occlusion. The average elevation was 12-15 mm. Hg. Presumably, owing to local vessel damage produced by the clamping, this pressure elevation continued after release of the clamp in several experiments. The initial rise in pressure which followed clamping of the internal mammary arteries was evident within one to five minutes in all experiments (Fig. 2). Systemic arterial pressure remained constant.

II. Free flow from the fine tubing which represented the pericardophrenic artery increased 50% to 100% with "internal mammary artery" clamping (Fig. 3). These values were obtained when the entire system was operated at a pressure head of approximately 50 mm. Hg. When determinations were carried out at 100 mm. Hg pressure head throughout the system, there was no appreciable increase in "pericardiophrenic artery" flow after clamping the "internal mammary artery" tubing. This finding was seemingly explained by the fine, nondistensible tubing used for the "pericardiophrenic artery," which would not allow a further increase in flow when operating at high pressures. Clamping of the tubing which represented the "internal mammary artery" produced a 50% to 100% increase in pressure within the "pericardiophrenic artery" tubing when the system was operated at the lower pressure head.

Comment

This project was not carried out to champion the cause of internal mammary artery ligation but, rather, was designed to furnish hemodynamic information which would tend to support or disprove the basic rationale of the procedure. Subjective evaluation of operative procedures carried out to alleviate the symptoms of myocardial ischemia is difficult, and frequently unsatisfying at best. The experimental approach is admittedly performed under laboratory conditions and with an essentially nonsclerotic vascular system but allows evaluation of hemodynamic principles.

The consistent elevation of subclavian artery pressure noted following internal mammary artery ligation in Part I indicates a favorable alteration in the basic relationship of F is equivalent to $\frac{P}{R}$. Other experimental investigations suggest that R (resistance) does not increase.[10] Whether this alteration is sustained and could be expected to be of lasting clinical benefit was not eval-

uated. Reduced intra-arterial pressure distal to sites of clinical coronary artery obstruction could be expected to enhance the increased operative pressure-gradient change from the pericardiophrenic artery to epicardial vessels. Theoretically, this would result in increased blood flow through these collateral routes, at least temporarily.

The semirigid plastic-tubing reproduction of the internal mammary-pericardiophrenic artery system used in Part II does, of course, utilize an unphysiologic fixed resistance. It is interesting, however, to note that the pressure alterations produced by "internal mammary artery" clamping in this system were of the same type as those elicited by the in vivo experiment (Part I). The increased "pericardiophrenic artery" flow which accompanied this pressure elevation was reproducible and of significant amount under the conditions described.

The data derived from these investigations support the basic rationale of the procedure insofar that it can be expected to result in increased blood flow through the pericardiophrenic artery. Whether this augmented blood flow traverses the tenuous collateral channels in the pericardial insertion onto the heart remains to be proved. Standards for clinical evaluation of this and other operative procedures used in treatment of arteriosclerotic heart disease are sorely needed. The patient with symptomatic coronary artery occlusive disease is particularly subject to emotional overlay and suggestion. It would, therefore, appear that a valid evaluation of these surgical procedures demands the use of adequate controls and/or random selection of patients. Only when a statistically significant number of patients have been managed in this manner shall we have a valid answer.

Summary

A series of subclavian artery pressure measurements have been made in dogs before and after bilateral internal mammary artery ligation. A consistent pressure elevation was noted. This finding is interpreted as representing a favorable alteration in the flow-pressure relationships of the internal mammary-pericardiophrenic artery system.

Utilizing a plastic-tubing reproduction of the internal mammary-pericardiophrenic artery system, pressure and flow determinations were made prior to and after "internal mammary artery" ligation. Both flow and pressure in the "pericardiophrenic artery" were increased by this procedure.

These investigations indicate that internal mammary artery ligation can be expected to increase blood flow through the pericardiophrenic artery. Whether this augmented flow is lasting and perfuses the myocardium in sufficient amount to be of clinical significance remains to be demonstrated.

Thoracic Surgical Division, Henry Ford Hospital.

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DISCUSSION

DR. R. MORTON BOLMAN, Fort Wayne, Ind.: I apologize for giving this discussion, for my partner, who is here, should really be giving it. We have had an intense interest in the problem of coronary insufficiency for some time, and we have done 35 internal mammary artery ligations—the first one about a year ago on a man who was receiving 100 mg. of meperidine every four to six hours, and was on bed rest because of precordial pain. He had an associated aortic stenosis. Dr. Lloyd ligated his internal mammary arteries a year ago. The man is still alive and is able to walk several blocks.

The interesting part of the procedure is that the mortality up to now is zero, and none of these 35 patients has died of coronary disease during the year. One of the drawbacks of this procedure, we feel, is that it is too simple. It is an operation that should be done late in the afternoon, when one's colleagues are not present, because it is so simple that they will all be doing it shortly.

One of my best personal friends had a severe infarction and was unable to walk across the room without severe pain. Prior to the advent of the internal mammary ligation, I did a Thompson operation on him, the talcum poudrage, and he got about 50% relief but had persistence of pain in his left hand and arm. After internal mammary ligation, he was back at work in his barber shop in 10 days and at the moment is symptom-free.

As we all know, there is a very appreciable mortality with the Beck procedure, and there is a certain amount of mortality with any procedure that opens the thorax. I merely rise to report that up to now we have done 35 of these ligations without mortality.

DR. HENRY SWAN, Denver: I must confess that I find myself very skeptical of the results reported by Dr. Szilagyi and his group, because in our laboratory we have been unable to demonstrate a rise in general systemic pressure, using an inlying needle with a string-gauge manometer placed in the aorta, in any ligation of a major vessel which we have done (and this has involved the femoral and the subclavian arteries). We have not ligated the internal mammary artery, as we thought such a small vessel would not produce a rise in systemic pressure. One can ligate the femoral artery in the dog or the subclavian artery in the dog and in man and find that there is no rise in the arterial pressure in the aorta.

For that reason, I should like to ask whether there is any explanation offered for a rise of pressure in the subclavian artery as measured by this particular technique when one ligates a vessel as small as the internal mammary artery.

I should also like to ask whether, in any experimental preparation that the group knows about, it is possible to demonstrate in vivo an actual increase in blood flow in any peripheral artery if one ligates a branch of that artery proximally.

This system which the authors described (in which there is so much interest) is too small to apply a blood-flow measurement to. The pericardial and phrenic arteries do not lend themselves to any method of measuring blood flow that we are aware of.

The group has just mentioned that they were unable to do this, and had to resort to a plastic model—a model which, however, lacks one very important and, I think, critical physiologic property, namely, the capacity to adjust its own peripheral resistance to changes in blood flow through any part of it.

We still remain extremely skeptical that any evidence has been presented showing that the flow of blood through any branch of the arterial tree will be significantly altered by the ligation of any other branch of the system.

DR. D. EMERICK SZILAGYI, Detroit: I come to the platform merely to clarify a statement.

Dr. Swan referred to this work as that of "Dr. Szilagyi and his group." Actually, this is entirely Dr. Taber's work, and I have been merely its sponsor for the program committee. I know it has been done very carefully, and, as far as it goes, it is accurate; but I fully agree with all the limitations Dr. Swan mentioned.

DR. RODMAN E. TABER, Detroit: Actually, we probably undertook this investigation in an unscientific manner, for it was done with the idea of being able to show that there was no logical reason for this phenomenon to occur. Like Dr. Swan, I am still skeptical.

In answer to Dr. Swan's inquiry regarding pressure measurements: Actually the description and, I am sure, the diagrams were somewhat misleading in that we felt we were measuring pressure alterations in the internal mammary artery by leading the catheter to the orifice of this vessel, rather than demonstrating systemic arterial elevations. I am sure aortic pressure changes would not occur with this type of operative procedure.

Finally, the operation of internal mammary artery ligation has evoked so much emotion, that if it accomplishes nothing else, it will result in a more critical evaluation of all the operative procedures for arteriosclerotic heart disease, certainly the selection of patients and the controls. If it succeeds only in doing this, it will make a major contribution.

Effect of Cigarette Smoke Tar on the Hamster Pouch

CONDICT MOORE, M.D., and A. JAMES MILLER, M.D., Louisville

Introduction

Many attempts are being made to investigate the precise role of tobacco in the occurrence of cancer of the human mouth, throat, and lungs. This work has been stimulated by recent experimental studies and epidemiological data,[1-4] the latter pointing to some significant etiological association between tobacco and these cancers. Such an association also has been demonstrated between mouth and throat cancer, the excessive consumption of alcohol, and certain states of chronic malnutrition, such as the Plummer-Vinson syndrome.[5-7] However, tobacco maintains the most consistent association with mouth cancer, as compared with alcohol and diet. Since cigarettes are by far the most widely used form of tobacco in this country, we became interested in studying the effects of cigarette smoke tar in experimental animals.

Materials and Methods

We have selected as our experimental tissue the oral pouch of the golden hamster (Mesocricetus auratus) because of its proximity to the mouth, its accessibility, and a dearth of previous work in inducing primary tumors of the pouch. We have also treated the skin of BALB/c mice, which we mention in this report as evidence of the relative carcinogenicity of the agents used on the hamsters.

A cigarette-smoking machine was designed to simulate human smoking habits. The machine produces about 1 gm. of tar per 35 cigarettes at an average temperature of 700 C at the center of the coal and at the height of the puff. The machine employs three puffs of smoke per minute, two seconds for each puff, with 30 cc. of smoke produced per average puff. Twenty cigarettes are smoked at one time, and we have used a standard brand of regular size. Cigarettes were smoked to a 1 cm. length. Tar was collected on the average of every two months and was used without addition of acetone or other solvent.

Fig. 1.—Benzpyrene, cigarette-smoke-tar, and plain wads ready for insertion into pouches.

Cotton and gauze wads, 1 cm. in diameter, impregnated with 440 mg. of pure tar without solvent, were secured with a single silk suture into the extremity of the right oral pouch of 80 hamsters, averaging 3 months of age. Intraperitoneal pentobarbital (Nembutal) anesthesia was used. Thirty control animals with plain wads were observed simultaneously, and twenty animals had treatment with similar wads soaked in 3,4-benzpyrene * in a 0.05% solution of sesame oil. These wads were often extruded at varying intervals and were promptly replaced when found to be absent. The average animal, living two years, had eight such replacements.

Ninety-six BALB/c mice were painted three times a week on the shaved back skin with pure cigarette smoke tar without solvent, 40 mg. per application. Twenty mice were painted three times a week with benzpyrene solution.

A smaller group of hamster pouches were painted with cigarette smoke tar three times a week. A

From the Departments of Surgery and Pathology, University of Louisville School of Medicine.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

Work supported by Grant No. C-2335 from the Grants Division, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Washington, D. C.

Dr. William Christopherson, Professor of Pathology, made suggestions during the progress of this work, and Mr. John Hagan and Miss Hazel Short gave technical assistance.

* Benzpyrene was provided by Distillation Products Industries, Division of Eastman Kodak Company, Rochester, N. Y.

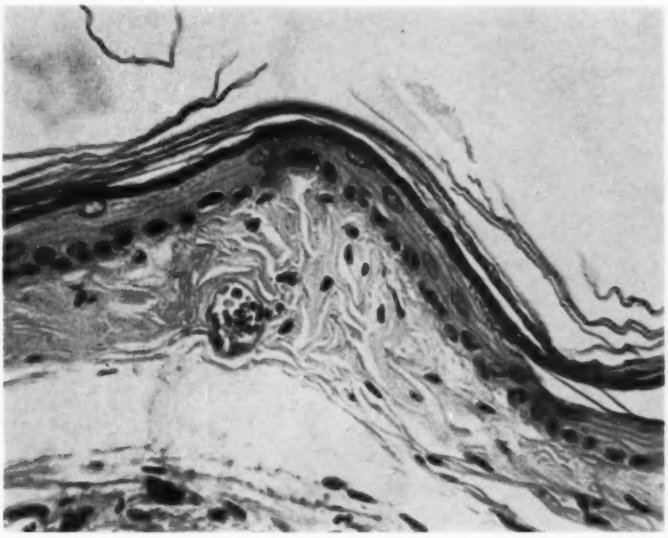

Fig. 2.—Microphotograph of untreated pouch in an animal 33 months old. Essentially no change.

few animals had pure benzpyrene powder placed into their pouches three times a week.

Animals were kept in separate cages. The right pouch of each hamster was used for treatment; the left pouch was untreated, as an additional control. All animals were observed every other day and were treated until they either died or were killed because death was imminent. Autopsies were performed on all; sections of most hamster pouches were obtained, including pouches treated for each monthly interval from 1 to 24 months, plus a few left-sided, control pouches. Both hamsters and mice were fed on Purina Laboratory Chow, with water freely. No fresh greens were given.

Results

Of the 80 hamsters treated with tar wads, 55 survived treatment for a year or more. Of these, 40 were treated for over 18 months, and 10 were treated for 24 months or more. One animal survived treatment for 30 months. In these tar-treated animals no tumors developed. The histologic changes in the treated animals are shown in the accompanying Table. They consisted of thickening of the epithelium, slight chronic inflammatory reaction, thickening of the lamina propria, and occasional hyperplasia of the basal-cell layer.

Of the 30 control animals treated with plain wads, 24 survived more than a year, and 7 of these lived from 18 to 25 months. Epithelial changes were occasionally present but were less marked than in the treated animals (Table).

Among the 20 hamsters treated with benzpyrene wads, 16 lived more than one year, and 6 of these survived from 18 to 23 months. The changes in these pouches generally resembled those in the tar-treated pouches except that a greater proportion of animals showed change and basal-cell-layer hyperplasia was more frequently found. No tumors were produced.

Summary of Histologic Findings in Hamster Pouches

Type of Treatment	Pouches Studied Microscopically	Duration of Treatment, Mo.	Pouches Showing Any Change	Pouches Showing Specific Changes			
				Lamina Propria Thickening	Epithelial Thickening	Chronic Inflammation	Basal Layer Hyperplasia
Plain cotton wad	23	2–25	4 (17%)	3	4	3	0
Benzpyrene cotton wad	12	5–23	9 (75%)	9	7	6	4 (33%)
Tar cotton wad	55	1–30	32 (60%)	24	25	23	6 (11%)
Control untreated left pouches	9	22–27	1 (11%)	0	1	0	0
Tar-painted pouches	13	11–16	6 (46%)	6	5	3	0

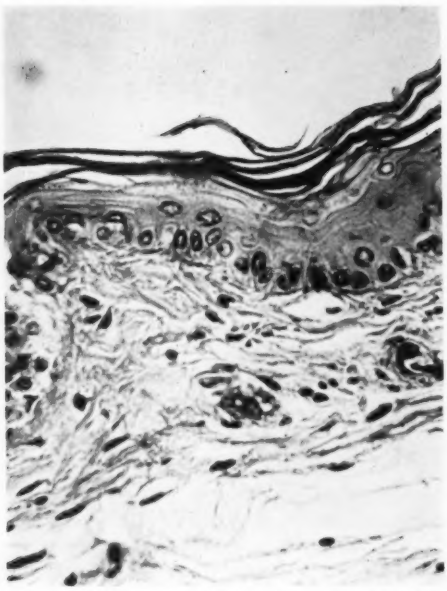

Fig. 3.—Microphotograph of pouch with plain cotton wad in place for 20 months. Slight epithelial thickening.

No correlation between the length of time these various wads remained in place over one year and the degree of changes produced was found in any group. In other words, most pouches treated for 24 months did not show noticeably greater changes than those treated for 12 months.

No tumors, but similar changes, were obtained in the small group of hamster pouches painted with cigarette smoke tar. Among several animals treated with pure benzpyrene powder, 50 mg. three times a week, one animal developed a gross tumor at 13 months. This has been called a noninvasive squamous-cell carcinoma.

Of the 96 tar-painted mice, 50 survived more than a year, and 20 survived more than a year and a half. Of these 50, one animal developed squamous-cell carcinoma of the skin at 14 months, and a second animal developed a similar cancer at 18 months. These two animals were killed at this time. Many of the animals developed papillomata at about two months after treatment was begun, but these disappeared within a month to six weeks later.

Twenty mice, painted thrice weekly with benzpyrene solution, all developed cancer in three to four months.

No spontaneous hamster pouch tumors have been observed in any of our animals.

Comment

There are many possible reasons for our failure to produce tumors in the hamster pouch. We shall discuss a few.

1. The method of implantation of a cotton wad in the hamster pouch was selected be-

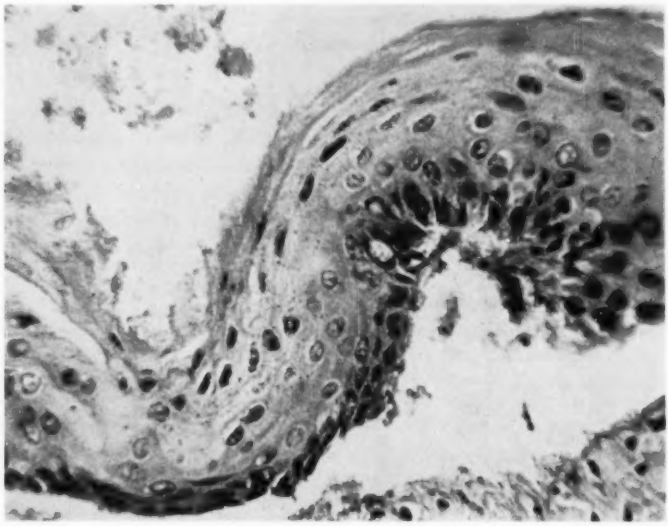

Fig. 4.—Microphotograph of pouch with benzpyrene wad in place 15 months. Epithelial thickening and slight basal-layer hyperplasia.

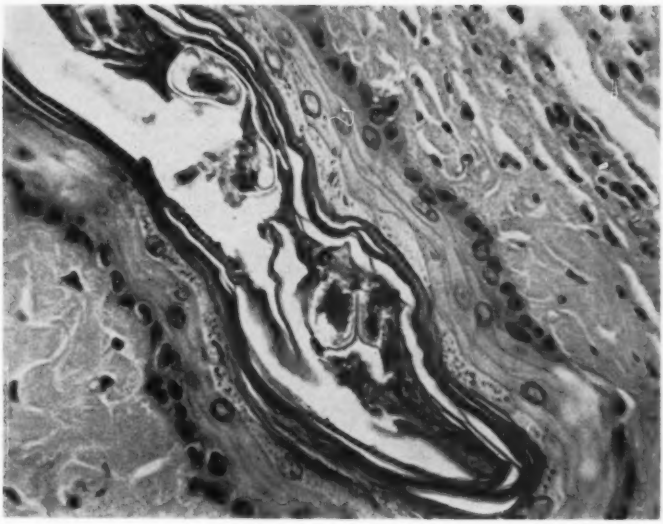

Fig. 5.—Microphotograph of pouch treated with cigarette-smoke-tar wad for 27 months. Some epithelial thickening and thickening of lamina propria.

cause we wanted a continuous contact of the agent with the pouch lining. Trials with various low-melting-point, tar-impregnated paraffin pellets were unsuccessful because of difficulty in keeping the pellets in place for long periods of time. We feel that our present cotton-wad method is the best we can use to achieve constant contact of agent with surface epithelium only, in spite of the fact that after a day or two the wad often becomes coated with a somewhat slimy layer of mucus and detritus. Our gross impression is that the impregnating agent in the cotton wad reaches the epithelium of the pouch after the first day or two only in a highly dilute solution of saliva or ingested water. Thus our wad-in-pouch method may be inadequate.

Fig. 6.—Microphotograph of pouch treated with cigarette-smoke-tar wad for 27 months plus 3 months of daily tar painting. Basal-layer hyperplasia. This is the most pronounced change in any tar-treated animal.

2. We must also consider the possibility that tobacco, in any form, will not produce hamster-pouch tumors at all. Moore and associates [8] have also failed to produce tobacco tumors in this pouch; we cannot find evidence of any other such work. However, we are planning to try other methods.

3. A number of investigators have studied the importance of sebaceous glands and hair follicles in skin carcinogenesis in animals.[9-12]

We have felt that, similarly, in the oral structures the mucous glands of the mucosa might play a part in mucous membrane carcinogenesis. The lack of mucous glands or any accessory epithelial structures in the hamster pouch might make it more difficult to produce tumors on this surface. However,

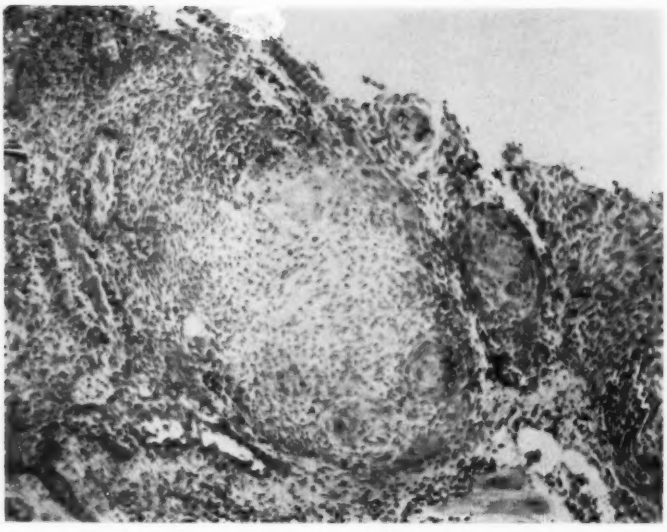

Fig. 7.—Microphotograph of noninvasive squamous-cell cancer produced by application of pure benzpyrene powder to pouch for 13 months—the only true tumor produced.

Salley does produce pouch tumors with several carcinogenic hydrocarbons and feels that accessory structures are not important. Goldhaber's observations on mouse oral mucosa, a resistant surface, by means of fluorescence microscopy, fail to show concentrations of the powerful chemical carcinogens in the mucous glands. The question of the importance of mucous glands in oral carcinogenesis thus remains an open one.

4. The possibility that the hamster pouch possesses an innate resistance to tumor growth occurs to us. The skin of the golden hamster appears much less susceptible to the production of tumors from strong carcinogens than that of many strains of mice. Our benzpyrene solution produces skin cancer in three months in mice, whereas Schinz and Fritz-Niggli [15] required an average of 15 months to produce cancer in the hamster

Fig. 8.—Gross appearance of pouch in Figure 2 (×5).

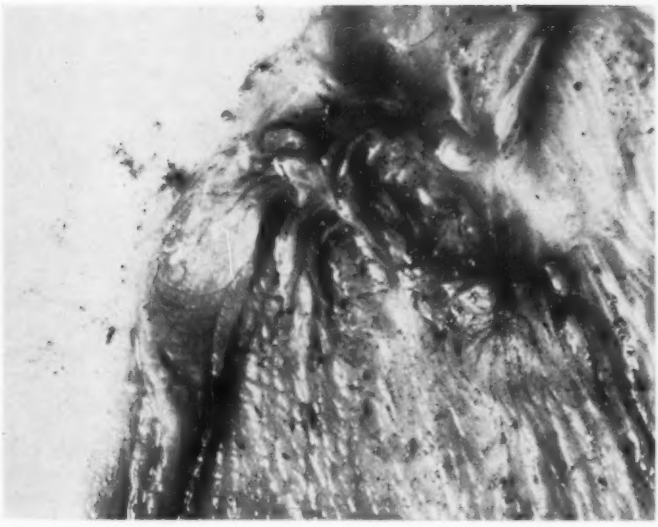

Fig. 9.—Gross appearance of pouch in Figure 6 (×5). Scarred points resembling healed ulcers represent suture sites. Wrinkling and fissuring are due to subepithelial fibrosis. This degree of gross change was unusual.

skin. Perhaps the hamster pouch shares this apparent species resistance of the hamster skin.

On the other hand, Salley [13] has produced cancer in hamster pouches in about five weeks with concentrated liquid petrolatum U. S. P. solutions of strong carcinogens. We have also produced one true tumor with pure benzpyrene powder. Therefore, the hamster pouch must be a susceptible surface.

5. Our failure to produce tumors with the cotton-wad method may stem from our using no solvent or from lack of primary trauma to the epithelium. The susceptibility of previously traumatized, regenerating tissue to carcinogenesis has been emphasized by Cramer and Stowell.[16-18] Also, Salley mentions that his solutions first caused pouch ulceration, later tumor formation. However, Berenblum discounts solvents and trauma as important factors in animal carcinogenesis.

6. It is of some interest to compare the relative carcinogenicity of 3,4-benzpyrene and cigarette smoke tar. In the mouse skin the average time of treatment for cancer production was about three and a half months with benzpyrene as compared with 16 months with tar. (Of course, there is a large difference in the percentage of animals developing tumors.) Considering treatment time alone, if tumors are to develop, they will take roughly five times as long to occur with cigarette tar as with the hydrocarbons. This agrees, in general, with Wynder's findings.

7. We may try to answer the question of the likelihood that animals will develop tar

Fig. 10.—Cigarette-smoke-tar wad shown in place in an everted hamster pouch. The thin pouch has been folded back on itself to allow one wad to be half exposed to view.

tumors if they live long enough, that is, into old age. Ten hamsters survived treatment for over two years, several living to an age of nearly 3 years. There was no suggestion of new or more advanced changes in these rather old animals.

A discussion of other factors that might affect animal carcinogenesis will not be attempted here.

From a different and more general point of view, we feel that a study of factors influencing susceptibility to cancer of oral surfaces will prove the fundamental and effective approach to the control of mouth cancer. We know that human mouth cancer occurs occasionally in the complete absence of the use of tobacco. Therefore, tobacco is not an essential factor in producing squamous-cell cancer of the mouth. Furthermore, while epidermoid mouth cancer nearly always occurs in the presence of tobacco, millions of people do use tobacco in various forms and to various degrees and never acquire mouth cancer. (Perhaps, as a rough estimate, of 100 smokers all of whom live and smoke for 50 years, probably only 1 will develop mouth cancer.) Therefore, the most important question, it seems to us, is this: What makes a certain few persons susceptible to this type of cancer, or susceptible to the tumorigenic effect of external irritants?

Summary and Conclusions

By the method used, whole cigarette smoke tar alone does not appear to be carcinogenic for the hamster oral pouch.

A number of factors which may influence the production of hamster pouch tumors are discussed.

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DISCUSSION

DR. WILLIAM M. CHRISTOPHERSEN, Louisville, Ky.: I think you will all agree that Dr. Moore deserves considerable credit for this work, in spite of the negative results.

In view of the fact that Dr. Moore is from Louisville, where the tobacco industry is similar to the smelting industry in Salt Lake City, it takes a brave man to do experimental work with tobacco tars.

The Tobacco Commission will be very happy to learn that tobacco does not produce cancer in the hamster. I am sure this will be publicized and that many people will draw the conclusion that it is not carcinogenic to humans or mice.

There are so many factors involved that Dr. Moore did not have time to discuss. For instance, many of the carcinogens, such as the polycyclic hydrocarbons, various radioactive materials, the aniline dyes, and so on, do not produce cancer in every person who is exposed to them. Thus, all chimney sweeps do not get cancer of the scrotum, nor do all smokers get cancer of the lung. There are many, many factors involved, and the individual susceptibility must be important. The presence or absence of infection or local tissue damage that might be present certainly does help to determine whether or not the animal will develop cancer.

In defense of the smoking machine, when Dr. Moore said he wanted to do some work on tobacco tars, both of us went to one of the tobacco companies and told them we were willing to do this work. They had a beautiful smoking machine which could be reproduced for about $1100. We suggested that they furnish the machine. They didn't care to. Dr. Moore had $7 and I had $3; and so we got together, designed this machine, and built it, as you saw in the slide.

I might say that, in spite of the "haywire," appearance of the machine, it was checked fairly carefully. The burning cigarettes were checked for temperature. The puffing on the machine was regulated to simulate, as far as possible, the puffing of a human on a cigarette. We tried as much as possible to simulate human smoking.

Dr. Moore in his work, of course, did not use a vehicle, a co-carcinogen, and did not traumatize the mucosa of the hamster's pouch.

In conclusion, I think it is important to point out that these findings should not be considered evidence that tobacco is not in some way carcinogenic in human beings. I think we might say that the hamster can use tobacco more safely than can humans.

DR. WALTER BURDETTE, Salt Lake City: Dr. Moore is to be complimented on the rather unique method which he has described for applying carcinogens over a long period of time.

Something should be said, however, about the clinical evidence obtained in India as to the carcinogenicity of tobacco. Betel-nut chewers also include tobacco, slaked lime, and various spices in the "pan," which often is held constantly in the cheek. Cancer of the oral cavity is the commonest of malignant tumors in India, and tobacco has been implicated as a promoting factor from clinical evidence, including the smoking and chewing habits of various social and religious groups in relation to the distribution and incidence of cancer.

This evidence has been presented in convincing form by Khanolkar, Paymaster, and their colleagues at the Indian Cancer Research Centre and Tata Memorial Hospital in Bombay, where interesting studies are currently in progress on the possible carcinogenicity of various fractions of Indian tobacco tars.

DR. RUDOLF J. NOER, Louisville, Ky.: Although I am not a co-author, I think it should be mentioned that Dr. Christophersen (as I am sure you gathered from the discussion) had a large part in this work. He said he thought it would be better in a surgical meeting that he, a pathologist, not be listed as a co-author; but he did have a large part in the work that Dr. Moore has reported to you this morning.

One thing that might be emphasized, which has already been pointed out, is the factor of individual variation, and also of species variation. I am reminded of a favorite story of a famous physiologist many years ago, whose son was being given a course in so-called health and hygiene in high school that included a talk about the evils of drink. The boy was shown an inflamed stomach of a dog and was asked what he thought about it. The physiologist, himself a teetotaler, was delighted with his son's reply: "It shows that alcohol is bad for dogs' stomachs."

As Dr. Moore and Dr. Christophersen have said, this tobacco apparently is not bad for hamster pouches.

It is particularly interesting that even among the hamsters, as one of the sections you saw this morning showed, some of the animals showed more susceptibility to this irritant than did others.

Until we can put our finger on the matter of individual susceptibility or, perhaps I should say, on the individual resistance to cancer, I am sure we shall continue to be in the dark about this very perplexing problem.

Use of Intravenous Fat Emulsion in Management of Surgical Patients

PAUL H. JORDAN Jr., M.D., Los Angeles

Although it is unlikely that the superiority of adequate oral nutrition will never be excelled by intravenous feedings, alimentation via the gastrointestinal route is frequently impossible, if not actually detrimental. Under these conditions one must resort to intravenous feedings. In spite of the progressive effectiveness of nutrition by this means, complete parenteral alimentation has been limited by our inability to administer adequate calories in a volume of fluid that is practical. The high caloric equivalent of fat, as well as other possible, essential metabolic functions of this nutrient, has stimulated efforts to produce a fat emulsion that can be administered with safety and without discomfort to the recipient.

Although it has been demonstrated in experimental animals [4,8,9] that intravenous fat is utilized, similar investigations in man [3,5,14-16] have been less extensive because of difficulties in obtaining fat emulsions consistently free of side-effects. The purpose of this paper is to report patient tolerance to the intravenous administration of an improved fat emulsion, Lipomul (I. V.), to demonstrate its stability after 18 months of storage, and to describe its metabolic effects when used as an adjunct to complete intravenous alimentation in man.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

This work was supported by grants from the Upjohn Company, Kalamazoo, Mich.; Mead Johnson & Company, Evansville, Ind., and Don Baxter, Inc., Glendale, Calif.

From the Departments of Surgery, Wadsworth General Medical and Surgical Hospital, Veterans' Administration Center, Los Angeles, and the University of California Medical Center.

Materials and Methods

The composition of fat emulsion used in these studies, Lipomul (I. V.), of the 11-612 series manufactured by The Upjohn Company, has been described previously.[7] Lipomul was stored at 40 F except during shipment from the manufacturer and certain special conditions, to be mentioned subsequently. The majority of infusions consisted of 600 ml. of Lipomul and were administered at an average rate of 266 ml. (40 gm. of fat) per hour. The maximum rate of 375 ml. of Lipomul (56 gm. of fat) per hour occurred by accident in one patient and resulted in a febrile reaction of 103 F. This patient developed no febrile reaction to 29 other infusions administered before and after the febrile episode. Forty infusions of 1200 ml. of emulsion were made in eight patients; the average rate of infusion was 300 ml. (45 gm. of fat) per hour for four hours.

The patients studied represented a wide spectrum of medical and surgical illnesses, including seriously ill postoperative patients. The inclusion of 25 cases of cirrhosis was the only intentional effort to select patients on the basis of their medical status. These patients were studied because of poor results obtained with a different emulsion employed in a similar group of patients.[6] The results of the infusions in this group are included in the total experience with fresh emulsion and are not considered separately.

Infusions were discontinued if any significant reaction developed. The pulse, respiratory rate, and blood pressure were measured at the beginning and end of each infusion and more frequently if indicated. All objective signs and subjective complaints that occurred during infusions and for the succeeding 24 hours were recorded.

The temperature was recorded at the beginning, the end, and 2, 4, 8, 12, and 18 hours after infusion. In order to obtain a numerical expression of the duration, as well as the height, of the febrile responses associated with infusions of fat emulsion, a "fever index" was calculated by a modification of the method of Beeson, as previously reported.[7]

The optical density method described by Mueller[12] for measuring serum turbidity was employed for estimating and following the degree of lipemia after intravenous fat infusions.

Indwelling catheters were placed in an arm vein of three patients undergoing 15-day metabolic studies with complete intravenous alimentation. The catheter was connected to a bottle of protein hydrolysate†; the tubing delivering fat emulsion was inserted into the catheter near the arm. Administration of the daily allotment of food substances, electrolytes, and vitamins required 24 hours. The patients were ambulatory throughout the studies.

Total nitrogen excretion in the urine and feces of patients undergoing metabolic studies was measured by a micro-Kjeldahl method. Sodium and potassium determinations were made using a flame photometer. Normal laboratory values for studies performed upon patients undergoing investigation were as follows: serum urea nitrogen, 8-17 mg. per 100 ml.; serum sodium, 135-150 mEq.; serum potassium, 3.5-5.5 mEq.; serum chloride, 98-107 mEq.; CO_2 capacity, 20-30 mEq.; 45-minute sulfobromophthalein (Bromsulphalein) retention, 5-7%; serum albumin, 3.5-4.0 gm. per 100 ml., and serum globulin, 2.4-4.0 gm. per 100 ml.

Procedures and Results

Reactions.—To ascertain the reaction rate with 600 ml. infusions of Lipomul and to avoid the difficulties of interpretation created by concomitant administration of other types of intravenous therapy, 323 nontherapeutic infusions were made in 259 patients who received no other intravenous therapy on the day of fat administration. First infusions of fresh (approximately two-month-old) Lipomul from seven lots were administered to 121 patients (Group 1). First infusions of seven-month-old Lipomul from one lot stored approximately six months at room temperature and one month under refrigeration were made in 37 patients (Group 2). Forty-five infusions in 19 patients were made with Lipomul from two lots aged 12 months, of which 4 months was at room temperature (Group 3). First infusions of Lipomul from three lots aged for 12 months were made in 72 patients (Group 4). Forty-eight infusions in 10 patients were made with 18-month-old Lipomul from two lots (Group 5).

TABLE 1.—*Effect of Storage of Lipomul upon the Incidence of Reactions Incurred with 600 Ml. Infusions*

	Age and Storage Conditions				
	2 Mo. (R *)	7 Mo. (1 at R 6 at RT †)	12 Mo. (8 at R 4 at RT)	12 Mo. (R)	18 Mo. (R)
No. of infusions	121	37	45	72	48
No. of patients	121	37	19	72	10
Chill	4	2		1	
Cyanosis	1				
Dyspnea	1				
Back pain		1			2
Flush	3	1		3	2
Headache	5	6	2	5	3
Nausea or vomiting	3	5	4	2	2
Cold feeling	1	2	2	2	
Fatigue		8	3	9	1
Arthralgia	3			2	
Dizziness	5	3	4	3	1
Anorexia		3	6	0	3
Abdominal pressure	3	3		2	2
Blurred vision	2	1		1	
No. of infusions without reactions	107	19	34	47	40
% of infusions without reactions	88	51	75	65	83

* R indicates refrigeration at 40 F.
† RT indicates room temperature.

Comparison of the number of reactions incurred with the use of Lipomul stored under various conditions is tabulated in Table 1. The incidence of infusions without reactions was 88% in Group 1, 51% in Group 2, and 65% in Group 4. The majority of reactions which occurred with increased frequency following infusions of aged emulsion were considered minor. It is noted in Table 1 that the incidence of infusions without reactions in Groups 3 and 5 approached the observed incidence of infusions without reactions in Group 1. Previous experience with consecutive infusions of fresh emulsion indicated that reactions were not apt to occur with successive infusions if they did not occur with the first. The data in Table 1 suggest that the subjective reactions which occurred with increasing frequency after the use of aged Lipomul were also less likely to develop with subsequent infusions if they were absent at the first infusion. Therefore, infusions of Groups 3 and 5 were not comparable to those in Group 1, since the latter were single infusions, whereas the

† Amigen was supplied by Mead Johnson & Company, and Hyprotigen by Don Baxter, Inc.

TABLE 2.—*Maximum Temperature Responses to Infusions of Lipomul Aged Under Various Conditions*

Age of Emulsion, Mo.	No. of Infusions	No. of Patients	Maximum Temperature, Degrees F				
			98.6	99.6	100.6	101.6	102.6 or Higher
			Per cent of Infusions				
2	121	121	41.5	34	18	5.0	1.5
7 *	37	37	30.0	54	16	0	0
12 †	45	19	18.0	64	9	4.5	4.5
12	72	72	18.0	60	14	5.5	2.5
18	48	19	20.0	63	16	2.0	0

* Six months at room temperature.
† Four months at room temperature.

majority of those in Groups 3 and 5 were repeat infusions in the same patients.

Of the seven patients (2.1%) in whom nontherapeutic infusions were discontinued, three patients had chills, three had colloid reactions, and one experienced a feeling of syncope. Of the four patients receiving fresh Lipomul when the infusions were discontinued, two had undergone major surgery, one had severe liver disease, and one had thrombophlebitis. Two infusions in Group 2 and one infusion in Group 5 were discontinued. The diagnoses in these cases were carcinoma of the pyriform sinus recently treated by irradiation, incisional hernia in an arteriosclerotic man aged 81, and varicose ulcer in a 53-year-old man.

The febrile reactions occurring in response to infusions of Lipomul are seen in Table 2. The maximum temperature elevation was 99.6 F or less in 75% to 88% of all infusions, regardless of the conditions under which the Lipomul was stored. The number of infusions with maximum temperatures in excess of 100.6 F was 6.5% in Group 1, zero in Group 2, 9% in Group 3, 8% in Group 4, and 2% in Group 5. The highest incidence (27%) of febrile reactions above 100.6 F occurred in a series of 25 patients with liver disease given fresh emulsion.

The average fever index for the five groups of infusions of Lipomul ranged from 4.3 to 6.5. Statistical analysis revealed no significant differences in the fever indices of the different groups.

Reactions associated with an additional 459 therapeutic infusions in 47 patients are tabulated in Table 3. The number of consecutive infusions received by each patient ranged from 2 to 30. Interpretation of the reactions encountered in this group was difficult because of concomitant administration of blood, plasma, protein hydrolysates, and/or some other therapeutic agent. Although every adverse effect was attributed

TABLE 3.—*Frequency of Reactions Associated with Consecutive Therapeutic Infusions of Lipomul in Forty-Seven Patients*

No. of infusions	Infusions									
	1	2	3	4	5	6–10	11–15	16–20	21–30	Total
	44 (3) *	45 (2)	42 (2)	39 (2)	36 (1)	105 (28)	57 (1)	20 (1)	31	459
Chill	1	1		2		3	2			
Back pain						1				
Headache	1	2	1	1	2	(5)				
Nausea or vomiting	3	1	1			2				
Cold feeling	1					2	1			
Fatigue or malaise	3	1				(3)	2			
Arthralgia	1			1		1				
Dizziness	3					3				
Anorexia	3	3	1	1	1	1				
Abdominal pressure		1	1		1		1	(1)		
Blurred vision					1					
Rash					1					
No. of infusions without reactions	34 (3)	39 (2)	40 (2)	38 (2)	32 (1)	96 (20)	52 (1)	20	31	410
% of infusions without reactions	79	87	95	98	89	87	91	95	100	89

* Infusions in parentheses are 1200 ml.; those not in parentheses are 600 ml.

for this reason to fat emulsion, 89% of infusions were without reactions. Further infusions were discontinued in six patients (12.7%) because of chills and fever. One debilitated patient with 18 in. of remaining small bowel developed a Staphylococcus aureus septicemia unrelated to fat emulsion, and a second patient developed cellulitis around a cut-down site. The causes for the adverse effects in the remaining four patients were unknown.

Disappearance Rate of Lipemia Following Consecutive Infusions of Lipomul.—Lipemia clearance studies were performed upon two patients receiving 30, and one patient receiving, 20 consecutive infusions of Lipomul (Table 4). Each infusion was begun between 8 and 9 a. m. and required 120 minutes for completion. The patients were permitted their regular meals. The optical density was measured before each daily infusion, and one, two, four, six, and eight hours after the start of every fifth to ninth infusion of the series. The sulfobromophthalein was measured periodically throughout the studies. Needle biopsies of the liver were taken at the conclusion of the series of infusions in Patients A. and B. Although the disappearance of lipemia was slower in B. and C. than in A., the optical density returned to preinfusion levels by the following morning in each case, with the exception of the sixth infusion in Patient C. The preinfusion optical densities performed on the days not reported in Table 4 were never elevated. The elevated sulfobromophthalein in B. and C. was consistent with observations made by others. There was no correlation between rate of clearing and degree of sulfobromophthalein retention, as had been expected. The sulfobromophthalein, elevated to 41% in B. at the conclusion of the infusions, declined to 29% by the ninth postinfusion day. Although no preinfusion liver biopsies were taken for comparison, examination of postinfusion liver biopsies revealed a greater accumulation of lipid in the liver from B. than from A. In addition, the brown-black pigment described by Mueller [13] in the reticuloendothelial systems was more abundant in B. than in A.

Use of Fat Emulsion in Complete Parenteral Alimentation.—Three male patients served as subjects. Experiment 1 was performed upon a 42-year-old man (D.) with chronic relapsing pancreatitis. This patient also served as subject for Experiment 2 three months after partial pancreatectomy. Experiment 3 was performed on a 61-year-old man (E.) with chronic, partial intestinal obstruction, and Experiment 4 was performed on a 40-year-old man (F.) who was

TABLE 4.—*Effect of Twenty to Thirty Consecutive Infusions of 600 Ml. of Lipomul Upon Sulfobromophthalein Retention and Blood Lipid-Clearing Pattern in Three Patients*

Patient	Infusion	Optical Density of Blood, Hours After Start of Infusion							BSP* Retention, %
		0	1	2	4	6	8	24	
A.	1	0.04	0.45	0.52	0.20	0.09	0.06	0.03	7
	5	0.08	1.05	1.25	1.35	0.60	0.18	0.07	10
	10	0.06	0.61	0.65	0.25	0.11	0.07	0.04	
	15	0.05	0.85	1.00	0.65	0.64	0.22	0.04	15
	22	0.05	0.18	0.13	0.09	0.07	0.07	0.07	
	30	0.05	0.73	1.10	0.70	0.44	0.22	--	7
B.	1	--	0.79	1.25	1.18	0.93	0.28	0.14	9
	9	0.04	1.30	1.50	1.50	1.45	1.35	0.14	32
	16	0.20	1.20	1.50	1.50	1.40	--	0.14	47
	20	0.05	0.39	0.32	0.27	0.20	0.16	--	41
C.	1	0.06	1.60	1.8	1.30	.93	0.16	0.05	3
	7	0.80	1.25	1.5	1.35	1.15	0.78	0.07	
	13	0.05	1.25	1.8	1.55	1.45	1.25	0.05	6
	21	0.12	1.40	1.6	1.50	1.25	1.00	0.07	14
	30	0.11	0.90	1.6	1.50	1.40	1.25	--	14

* Sulfobromophthalein (Bromsulphalein).

TABLE 5.—*Summary of Metabolic Data from Three Undernourished Patients Fed Entirely by Intravenous Alimentation*

Experiment	Period	Days of Period	Total I. V. Calories (Ave/Day)	Calories from Fat (Ave/Day)	Mean N Intake (Gm/Day)	Mean N Balance (Gm/Day)	Difference Between Compared Means	*P*	Mean K Intake (mEq/Day)	Mean K Balance (mEq/Day)	Difference Between Compared Means	*P*	Mean Na Intake (mEq/Day)	Mean Na Balance (mEq/Day)
1 D.	1	5	1700	810	16	3.2±2.2	0.1	N. S.*	40	5.6±14.1	6.4	N. S.	106	—21.3±61.8
	2	5	2600	1620	16	3.3±0.5			40	12.0±6.4			100	33.6±10.8
	3	5	1700	810	16	2.7±1.8	0.6	N. S.	40	—11.9±9.6	23.9	<0.01	109	42.8±16.8
2 D.	1	5	1700	810	16	4.2±1.8	1.6	N. S.	40	— 9.2±6.5	2.5	N. S.	100	—40.1±40.4
	2	5	2600	1620	16	2.6±1.7			40	—11.7±4.8			100	13.7±18.1
	3	5	800	0	16	—0.4±2.4	3.0	<0.05	40	—23.2±14.6	11.5	<0.01	100	—16.4±21.4
3 E.	1	5	1700	810	16	2.0±1.1			40	— 8.1±15.5			100	13.8±22.6
	2	5	2600	1620	16	3.8±1.9	1.8	<0.05	40	— 5.2± 9.9	2.9	N. S.	100	16.9±28.1
	3	4	1700	810	16	4.6±2.0			40	—12.3±29.5			107	21.6±59.1
4 F.	1	5	1700	810	16	1.6±1.1	2.8	<0.05	40	3.8± 9.2	9.6	<0.05	115	— 8.0±69.9
	2	5	2600	1620	16	—1.2±1.3			40	— 5.8± 2.5			100	—34.4±23.3
	3	5	1700	810	16	—0.5±2.7	0.7	N. S.	40	—19.2±15.3	13.4	N. S.	103	—17.2±45.2

* Not significant ($P>0.05$).

unable to eat because of pain seven years after total gastrectomy.

Each experiment consisted of three five-day metabolic periods, except for Period 3 of Experiment 3, which was four days. In Experiments 1, 3, and 4, Periods 1 and 3 were identical. The daily intravenous diet in these periods consisted of 16 gm. of nitrogen, 124 gm. of carbohydrate, 90 gm. of fat, 40 mEq. of potassium, 100 mEq. of sodium, and vitamins B and C. The diet of Period 2 of Experiments 1, 3, and 4 were similar to Periods 1 and 3 except that the daily fat intake was increased from 90 to 180 gm.

In Experiment 2, injections of 50 mg. of nortesterionate (Depo-Nortestonate) were given daily during Periods 2 and 3. During

Fig. 1 (Experiment 1).—Metabolic balance study performed during complete parenteral alimentation of a malnourished 42-year-old man (D.) with chronic relapsing pancreatitis. Nitrogen, potassium, and sodium intakes are charted upward from the 0 line, and outputs are charted downward from the top of the intake line. An excess of output over intake is seen as a clear area below the 0 line. If output is less than intake, the difference is represented by a black area above the 0 line. Shaded areas designate caloric contribution of intravenous fat emulsion.

TABLE 6.—*Summary of Laboratory Studies Performed Before, Midway of, and at the Conclusion of Fifteen Days of Complete Parenteral Alimentation in Three Patients*

Experiment		Na, mEq.	K, mEq.	Cl, mEq.	CO_2, mEq.	Ca, Mg.	P, Mg.	BSP* (% Reten.)	A/G Ratio, Gm.	Hemoglobin, Gm.	Hematocrit
1 D.	Before	132	5.2	100	23.7	10.1	--	4	4.2/2.9	13.1	--
	Midway	130	4.9	96	24.2	6.8	--	--	--	13.1	41
	End	146	4.8	96	22.4	8.9	5.2	11	5.2/2.7	13.1	43
2 D.	Before	136	4.0	98	22.0	8.3	4.8	10	4.4/2.1	12.6	40
	Midway	142	4.9	93	18.1	8.9	1.5	--	5.5/2.9	14.0	43
	End	142	4.4	99	20.0	9.7	6.1	8	5.1/2.8	12.6	40
3 E.	Before	142	3.7	98	24.6	8.6	3.3	2	4.4/1.9	11.4	32
	Midway	130	3.2	93	24.6	7.3	6.0	3	4.8/2.5	12.1	36
	End	146	3.4	99	25.0	9.5	3.7	23	4.7/2.2	9.6	32
4 F.	Before	142	6.0	98	24.6	9.1	3.9	1	3.8/2.1	13.1	43
	Midway	138	4.9	91	--	8.9	5.9	--	4.1/2.3	14.7	39
	End	134	5.3	97	22.8	6.0	6.4	36	4.3/2.8	14.7	46

* Sulfobromophthalein (Bromsulphalein).

Period 3 the patient received no intravenous fat. With these exceptions, Periods 1, 2, and 3 were similar to the other experiments.

Table 5 is a summary of the metabolic data collected during the four experiments on complete parenteral alimentation. Table 6 is a summary of the laboratory studies performed before, midway of, and within two to three days of the conclusion of these experiments.

Experiment 1 (Fig. 1): During Period 1, the patient was in positive nitrogen balance, averaging 3.15±2.15 gm. per day. The potassium balance was also positive during the first period, averaging 5.6±14.1 mEq. per day. During Period 2, when the daily intravenous diet was altered by an additional 90 gm. of fat, the nitrogen and potassium balances remained positive, averaging 3.34±0.5 gm. per day and 12±6.4 mEq. per day, respectively. In Period 3, when the intravenous fat was decreased to 90 gm. per day, the average daily nitrogen balance was 2.72±1.8 gm., whereas the potassium balance for the same period was −11.9±7.5 mEq. per day.

Experiment 2 (Fig. 2): In Period 1, the mean daily nitrogen balance was 4.16±1.8 gm. and the mean daily potassium balance was −9.2±6.5 mEq. During Period 2, the nitrogen balance was not significantly affected by an increased fat intake and daily injections of nortesterionate. For this period the mean daily nitrogen balance was 2.57±1.7 gm. and the mean daily potassium balance was −11.7±4.8 mEq. per day. During Period 3, when the patient continued to receive 50 mg. of nortesterionate daily but was allowed no fat, the nitrogen balance was negative for the first time, averaging −0.37±2.4 gm. per day. At the same time, the negative potassium balance increased to −23.2±14.6 mEq. per day.

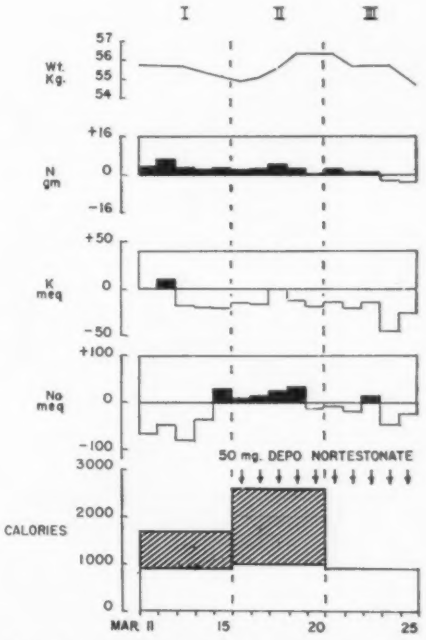

Fig. 2 (Experiment 2).—Study of the effect of intravenous fat upon nitrogen and electrolyte balances during complete parenteral alimentation of D. three months after pancreaticoduodenectomy.

Statistical analysis of the mean nitrogen and potassium balances for Experiments 1 and 2 are presented in Table 1. Except for the loss of 1.4 kg. during Period 3 of Experiment 2, the subject's weight remained relatively constant throughout both studies, showing a tendency to gain during the second period of both experiments. The patient had no significant temperature elevation and experienced no untoward reactions during either experiment. Actually, the patient derived during Experiment 1 the greatest relief of his pancreatic pain that was achieved by any medical management.

Experiment 3 (Fig. 3): Periods 1 and 2 were five days in duration, while Period 3 was terminated after the fourth day because of a febrile reaction. During Period 1, the nitrogen and potassium balances averaged 1.99 ± 1.05 gm. per day and -8.1 ± 15.5 mEq. per day, respectively. During Period 2, when the fat intake was increased to 180 gm. per day, the positive nitrogen balance increased significantly ($P<0.05$) and averaged 3.84 ± 1.9 gm. per day, whereas the potassium balance remained negative, -5.2 ± 9.9 mEq. per day. The mean daily nitrogen and potassium balances for the first three days of period 3 were similar to the results obtained in Periods 1 and 2. On the fourth day the patient's temperature rose to 105 F. The urinary sodium and potassium losses on this day were 9 and 103 mEq., respectively, compared with the average of 106 and 35 mEq., respectively, for the three preceding days. The nitrogen excretion on the fourth day unexpectedly increased to 5.08 gm. As an explanation of this finding, altered renal function secondary to the febrile episode was suggested by a blood urea nitrogen level of 30 mg. per 100 ml. three days after the reaction. Because of the febrile episode, the mean daily nitrogen balances for Periods 2 and 3 were not compared. Analysis of the mean daily nitrogen and potassium balances of Period 2 and the first three days of Period 3 revealed no significant differences. The subject's weight was stable throughout the study, and his only complaints were headaches during Period 2. The sulfobromophthalein increased from a preinfusion level of 2% to 23% on the day following febrile reaction. Nine days later the sulfobromophthalein had decreased to 10%. Other laboratory studies were essentially unchanged.

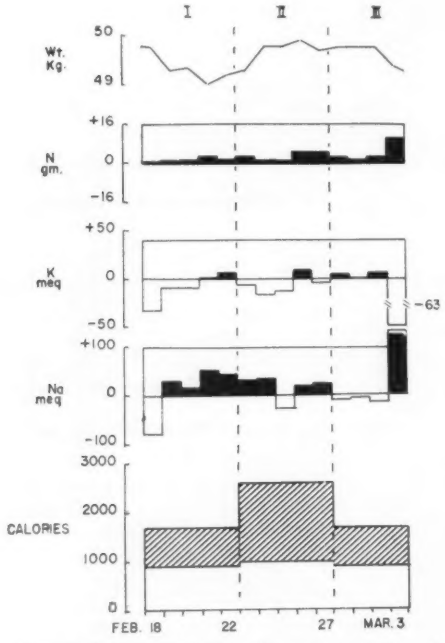

Fig. 3 (Experiment 3).—Comparison of the effects of 90 and 180 gm. of intravenous fat daily upon nitrogen and electrolyte balances in a 61-year-old man (E.) with chronic partial intestinal obstruction receiving complete parenteral alimentation.

Experiment 4 (Fig. 4): During Period 1, the nitrogen balance averaged 1.58 ± 1.1 gm. per day and the potassium balance averaged -3.8 ± 9.2. During Period 2, when the fat intake was increased to 180 gm. per day, the nitrogen balance became negative, averaging -1.18 ± 1.3 gm. per day, and the potassium balance remained negative, averaging -5.8 ± 2.5 gm. per day. The differences between the mean daily nitrogen and potassium balances for Periods 1 and 2 were statistically significant ($P<0.05$). During Period 3, when the fat intake was reduced

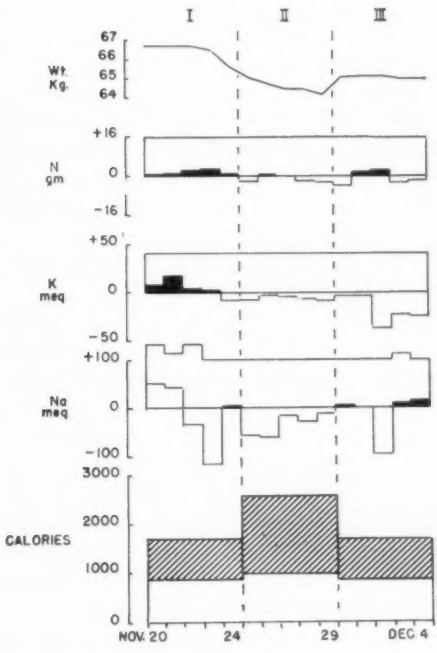

Figure 4

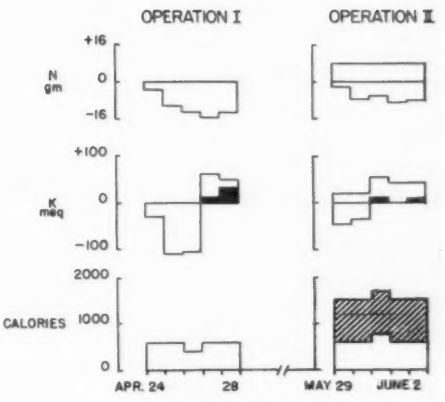

Figure 5

Fig. 4 (Exepriment 4).—Comparison of the effects of 90 and 180 gm. of intravenous fat daily upon the nitrogen and electrolyte balances in a 40-year-old man (F.), with total gastrectomy, receiving complete parenteral alimentation.

Fig. 5 (Experiment 5).—Comparison of the metabolic responses to bilateral transthoracic dorsal sympathectomy in a 37-year-old man on an inadequate caloric and nitrogen-free intake after the first operation and suboptimal caloric and nitrogen intakes after the second operation. Intravenous fat was the chief source of increased calories after the second procedure.

to that of Period 1, the negative nitrogen balance was reduced to -0.5 ± 2.7 gm. per day, while the negative potassium balance increased to -19.2 ± 15.3 mEq. per day. There was no significant difference between the mean daily nitrogen and potassium balances of Periods 2 and 3. The patient was afebrile throughout the study. He complained of malaise and fatigue during Period 2 but had no complaints during Periods 1 and 3. The most significant laboratory finding was an increase in the sulfobromophthalein from 4%, prior to the experiment, to 36%, at the completion of the study. Twenty-one days later this had returned to 4.6%. Weight loss was greatest during Period 2, when the patient was in greatest negative nitrogen balance.

Use of Fat Emulsion in Early Postoperative Cases.—Two male patients, aged 37 and 63, who underwent bilateral transthoracic dorsal sympathectomy and bilateral lumbar sympathectomy, respectively, served as subjects for Experiments 5 and 6. In each case the two operations were separated by approximately one month. For five days after each operation (day of operation inclusive), the patients were maintained on complete parenteral alimentation and were allowed nothing orally.

Experiment 5 (Fig. 5): After the first operation, the average daily intake of 560 Cal. was composed entirely of carbohydrates. The mean daily nitrogen balance for this period was -10.88 ± 4.5 gm., and the mean daily potassium balance was -39.7 ± 68 mEq. After the second operation, the average daily intake of 1541 Cal. was composed of 8 gm. of nitrogen, 90 gm. of fat, and 175 gm. of carbohydrate. The mean daily nitrogen balance was -6.34 ± 2.7 gm., and the average daily potassium balance was -10.7 ± 8.75 mEq. Statistical analyses revealed no significant difference between the average daily nitrogen or potassium balance for Operations 1 and 2 ($P<0.1$).

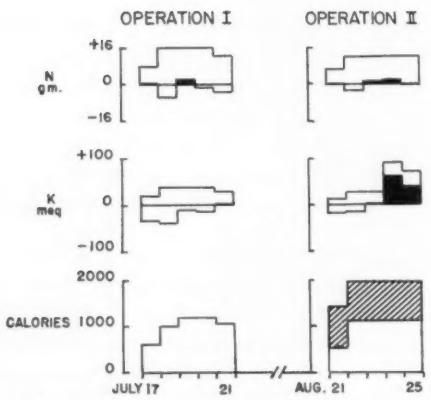

Fig. 6 (Experiment 6).—Comparison of the metabolic responses to bilateral lumbar sympathectomy in a 63-year-old man on suboptimal caloric and moderate nitrogen intakes after the first operation and moderate caloric and a suboptimal nitrogen intake after the second operation. Intravenous fat was the chief source of increased calories after the second procedure.

Experiment 6 (Fig. 6): After the first operation, the average daily intake of 1018 Cal., was composed of 13.6 gm. of nitrogen and 170 gm. of carbohydrate. The mean daily nitrogen balance for this period was -1.01 ± 2.9 gm., and the mean daily potassium balance was -17.27 ± 17.5 mEq. After the second operation the average daily nitrogen intake was decreased to 10.3 gm. and the average daily caloric intake was increased to 1881 by the addition of 90 gm. of fat per day. The mean daily nitrogen balance was 0.24 ± 1.6 gm. per 100 ml., and the mean daily potassium balance was 16.33 ± 33.1 mEq. There was no significant difference between the mean daily nitrogen balances after Operation 1 and 2. There was, however, a significant difference in the mean potassium balances of these two periods.

Comment

The wide range of medical and surgical conditions which preclude effective oral alimentation requires that parenteral feedings be made more effective. To achieve this goal, the need for a suitable intravenous fat emulsion has been apparent. Prior to the present era, the adverse effects associated with the use of available preparations restricted their application to clinical investigation. The remarkable reduction in the incidence of reactions reported with the introduction of improved Lipomul [7,11] suggested a substantial advancement in this field and provided encouragement that the development of an ideal fat emulsion is feasible.

The practicability of Lipomul for clinical use is attested to by the results obtained in a group of 259 patients who received 323 nontherapeutic infusions uncomplicated by the concomitant use of other intravenous materials. The over-all nonreaction rate with the use of Lipomul aged as long as 18 months was 74%. The majority of reactions were minor and did not seriously concern the patients. Colloid reactions developed in only three cases, and in none was the magnitude comparable to similar reactions encountered with previous emulsions.

Further evidence of the practicability and safety of fat emulsion as a therapeutic agent is evident by the absence of reactions in 89% of 459 therapeutic infusions in 47 patients. In six cases the infusions were discontinued because of thermogenic reactions. These resulted from septicemia unrelated to fat emulsion in two patients and for unknown reasons in four patients. The possible explanations in these cases included (1) defective emulsion (each patient received emulsion from the same lot), (2) "overloading" with fat emulsion, (3) breaking the emulsion by mixing with protein hydrolysate, (4) reactions to protein hydrolysates, and (5) infection. The emulsion used in these four cases was found satisfactory on retesting and was subsequently administered to three patients without reactions. One of the four patients subsequently received 30 daily infusions of emulsion to supplement his oral diet, and a second patient received 15 daily infusions of emulsion mixed with protein hydrolysates, as had been done previously. Neither patient exhibited untoward effects from the second series of infusions. These results

tend to eliminate all but infection as the cause for the reactions. Infection appeared most likely, even though not verified, since each patient received protein hydrolysates (administration time 12 hours per liter) through an indwelling venous catheter. These results indicate the meticulous care required in the administration of complete parenteral alimentation and suggest the inadvisability of allowing protein hydrolysates to be exposed for as long as 12 hours to room air, or of using indwelling venous catheters if they can be avoided.

A fat emulsion suitable for commercial production and wide clinical use must be sufficiently stable that its safety and toleration can be ensured after a reasonable period of storage. A comparison of the reactions to infusions of Lipomul kept under the various storage conditions of this study suggests that Lipomul fulfills these requirements for an acceptable fat emulsion. Aging, but particularly storage at room temperature, exerted an influence upon the incidence of subjective reactions but had no significant effect upon objective reactions. The increased number of subjective reactions associated with infusions of emulsion stored four to six months at room temperature is indicative of a developing imperfection in Lipomul with age which can be significantly arrested by refrigeration.

Utilization of fat emulsion administered intravenously has been demonstrated in animals by a variety of techniques. Similar investigations in man have been restricted to short-term studies because of reactions associated with the use of available preparations. The effectiveness of fat emulsion as an intravenous caloric supplement for an inadequate oral diet in man was described by Van Itallie[16] and Bentley.[3] Prolonged metabolic studies employing fat emulsion as a supplement to complete parenteral alimentation were performed in dogs.[10] The high degree of patient tolerance to Lipomul suggested the feasibility of similar long-term studies in man. The results of these studies indicated that nitrogen equilibrium can be maintained in patients for periods of 15 days by means of complete parenteral alimentation, including fat. Under the conditions of these studies it appeared that the metabolic advantage of increasing the fat intake from 90 to 180 gm. per day was slight. In fact, there was some suggestion that administration of the larger quantity resulted in a detrimental "overloading" with fat. "Overloading" may have contributed to the elevated sulfobromophthalein in Patients E. and F., the subjective complaints in both patients during Period 2, the febrile reaction in E., and the slight nitrogen deficit in F. during Periods 2 and 3. We agree with Watkin,[17] who reported that for prolonged administration the average 70-kg. man was able to handle about 100 gm. of fat per day intravenously.

The findings of negative potassium balances in Experiments 1 to 4 were unexplained. These results were not consistent with the potassium-saving effect of fat emulsion reported by Van Itallie[16] in patients on an inadequate oral diet receiving supplementary intravenous fat for short periods. The mechanism for the potassium deficits may be related to the fall in serum potassium reported by Becker,[2] although it was his opinion that the latter was probably the result of an intracellular transport mechanism rather than increased potassium excretion. The potassium deficits observed in our experiments suggest that with an intravenous regimen similar to the one employed, amounts of potassium in excess of 40 mEq. per day should be used. With the elimination of the potassium deficit, parenteral alimentation may be more effective in producing positive nitrogen balance.

With an intake of 47 Cal. per kilogram of body weight and 0.29 gm. of nitrogen per kilogram, the use of an anabolic hormone exerted no apparent beneficial effect upon nitrogen deficit in Period 2, Experiment 2. Its continued use during Period 3, when the caloric intake was reduced to 31 Cal. per kilogram, may have prevented a greater nitrogen deficit than occurred.

The use of intravenous fat in the early postoperative period has been described by Van Itallie,[16] Abbott,[1] and Shingleton.[15] While there is controversy concerning the feasibility or advisability of attempting to prevent or minimize nitrogen wasting by providing adequate nutritional intakes, the two reported cases which have served as their own controls support the opinion of those[1] who state that nitrogen deficits can be reduced by adequate nutritional intakes.

In Experiment 5, the patient received an inadequate daily caloric intake (8.6 Cal/kg.) and no nitrogen after the first operation, and suboptimal caloric (24 Cal/kg.) and nitrogen (0.13 gm/kg.) intakes after the second operation. Although there was no significant difference in the average daily nitrogen and potassium balances between the two operations, the five-day accumulative nitrogen loss decreased from 54.4 to 31.7 gm.

In Experiment 6, the patient received suboptimal daily caloric (14.5 Cal/kg.) and moderate nitrogen (0.2 gm/kg.) intakes after the first operation. After the second operation the patient's daily caloric intake (29 Cal/kg.) was increased by the use of fat emulsion and the daily nitrogen intake was decreased approximately 20%, to 0.16 gm/kg. Although there was no significant difference in the average daily nitrogen balances between the two operations, the five-day accumulative nitrogen balance decreased from -5.1 to $+1.2$ gm., even though the nitrogen intake had been decreased. The potassium balance, which was negative after the first operation, became positive after the second procedure, and the difference between the two periods was statistically significant ($P<0.01$). The results of Experiments 5 and 6 indicate that the nitrogen deficits in postoperative patients can be minimized by providing increased caloric and nitrogen intakes. These results, as well as the work of others, support the thesis that maintenance of an adequate caloric and protein intake in the early postoperative phase is preferable to the deficient regimens commonly employed.

Summary and Conclusions

Three hundred twenty-three nontherapeutic infusions of Lipomul were made in 259 patients to investigate the adverse effects associated with the use of this emulsion after storage. There was no appreciable difference in the number of reactions with fresh emulsion and that stored 18 months at 40 F. The reaction rate to Lipomul stored at room temperature from four to six months was less satisfactory than that to Lipomul stored under refrigeration. There were no significant differences in the febrile responses obtained with Lipomul stored under the various conditions.

An additional 459 therapeutic infusions were made in 47 patients. Of this number, 89% were without reactions. Infusions were discontinued in six patients because of reactions due to infection unrelated to fat emulsion in two patients and unknown causes in four patients. Although blood lipid clearance studies and sulfobromophthalein evaluation have not been useful thus far in predicting the onset of a reaction, daily infusions of fat emulsion should be temporarily discontinued if the blood remains lipemic or if the sulfobromophthalein increases significantly.

Contraindications to the use of fat emulsions have not been defined precisely, since the causes for reactions remain unclear and there are no methods for predicting the occasional case that will react to the emulsion. Because of our experience, which is contrary to that of others, we have avoided the use of fat emulsion in patients with serious liver diseases. We have also refrained from its use in obese patients and patients with severe collagen diseases. Cardiac disease, hypertension, or extrahepatic jaundice has not been a contraindication to its use.

Our experience with Lipomul indicates that it is safe for clinical use if administered with the ordinary caution usually afforded other types of medication. Its use is indicated as a supplement to an inadequate oral diet in malnourished patients, or as a high

calorigenic material for complete parenteral alimentation to be used over an extended period, or for short periods during the early convalescence of a postoperative patient.

Metabolic data from three patients maintained on complete parenteral alimentation indicated that nitrogen equilibrium can be maintained for 15 days by this means. The observation of a persistent negative potassium balance indicated that the potassium intake with a similar regimen should exceed the 40 mEq. per day used in these studies. In patients weighing between 55 and 60 kg., the possible detrimental effects resulting from "overloading" with fat appeared greater than the advantage accrued from administration of more than 90 gm. of fat per day.

Two patients, each of whom underwent bilateral operations performed at one-month intervals, received intravenous fat following the second operation and none following the first. The data on these patients, who acted as their own controls, suggested that the nitrogen deficits incurred following surgery can be minimized by the addition of adequate nitrogen and calories to the intravenous diet.

Although much remains to be learned about the routine clinical use of intravenous fat emulsion, the data presented support the conviction that intravenous fat emulsion can be administered with safety and benefit to a large segment of patients for whom adequate parenteral alimentation is vital.

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DISCUSSION

DR. ARNOLD STEVENS, Beverly Hills, Calif.: The data Dr. Jordan has presented seem to me both interesting and important. The results of this study suggest several pertinent considerations.

So far as I know, there has been no other parenteral therapy which has permitted a patient to remain in reasonably normal nitrogen and caloric balance for periods of as long as 15 days. From a practical standpoint, however, there are sufficient problems which remain unanswered in this study to preclude the routine use of fat emulsion by clinicians for so long a period of time.

On the other hand, the data which Dr. Jordan has submitted suggest that this form of therapy is feasible, safe, and beneficial for shorter periods of up to five days.

It seems to us, on the basis of this experience with fat emulsions, that this form of therapy may be a boon to the surgeon when he encounters patients with postoperative renal shut-down. In these patients proteins are, of course, contraindicated, whereas, so far as present data indicate, fat emulsions may be administered without untoward renal effects. This agent may be given in sufficient amounts to maintain adequate caloric intake without overloading the patient with water. Hazardous potassium elevation and protein breakdown are lessened.

DR. FREDERICK W. PRESTON, Chicago: Since it has been shown that intravenous infusions of fat cause accumulation of fat in the liver and spleen of experimental animals, it is important to know whether amounts of fat suitable for human dosage affect liver function or lead to accumulation of lipid substances in the liver. To settle this question, we have given daily infusions of 600 cc. of fat emulsion to 20 patients for approximately two weeks and have done a variety of liver function tests before, during, and after the courses of the infusions. The only liver function test significantly affected is the sulfobromophthalein retention test. The first slide shows sulfobromophthalein retention in 10 patients who had normal sulfobromophthalein retention before the infusion, in 6 of whom the retention was elevated between 5% and 15% and in 4 of whom the retention was above 15%. In each group there was increased dye retention during the period of fat infusion and return to preinfusion levels after the infusions were discontinued. In five of these patients, liver biopsies were done before and after the infusion of fat, and the tissues stained with a special stain for fat. There was no abnormal accumulation of fat in the livers of these patients. [Slide]

The third slide shows sulfobromophthalein retention and thymol turbidity in an additional patient who received 67 infusions, each containing 600 cc. of fat emulsion. On each occasion there was increased sulfobromophthalein retention during courses of the infusion, with return to preinfusion levels after the infusions were stopped. The thymol turbidity paralleled the sulfobromophthalein retention. No ill effects from this amount of fat infusion were noted in this patient.

DR. PAUL H. JORDAN JR., Los Angeles: Dr. Stevens has called attention to what may be one of the important indications for the use of fat emulsions in surgical patients. Personally, I have had insufficient experience to make any further comment about it.

As Dr. Preston pointed out, a number of people have noticed the increase in sulfobromophthalein with the administration of fat emulsion, but the sulfobromophthalein test is very difficult to interpret. There are many factors that can influence it, temperature being one of the most important.

We, too, have noted that the sulfobromophthalein usually will come back to normal in a short time. We have included in our paper a group of patients to whom we gave fat emulsion daily for 30 days, doing sulfobromophthalein retention tests every fifth day, and correlating the results with the rate at which fat disappeared from the blood. Although the sulfobromophthalein was elevated at the end of 30 days, the patients were able to clear the fat from their blood as rapidly on the 30th as on the 1st day. At the end of 30 days the liver biopsy specimens of these patients looked a little different than those described by Dr. Preston, in that there was a fair accumulation of fat.

What the significance of the sulfobromophthalein elevation in relation to fat administration is I cannot say, but we have steered away from patients with liver disease because of this factor, as well as the fact that this group of patients has contributed highest to the incidence of reactions. As a matter of fact, the discrepancy that occurs between the 88% of infusions without reactions, which I showed on the slide, and the 99% stated in the abstract is due to the fact that a group of 25 patients with liver disease was included in the former but was omitted in the latter. Patients with liver disease gave us our highest incidence of reactions—27%.

New Surgical Approach for Upper Thoracic Sympathectomy

A Method to Avoid Horner's Syndrome

LOUIS T. PALUMBO, M.D., Des Moines, Iowa

Introduction

For many years I have been dissatisfied with surgical approaches and techniques which were advocated for sympathetic denervation of the head, neck, shoulder, chest, upper extremity, heart, and coronary circulation. These left much to be desired, from the standpoint both of the surgeon and of the patient. Frequently the operation was difficult to perform and usually resulted in incomplete denervation, so that the desired physiologic changes did not occur. Moreover, the exposure was difficult and inadequate, making it impossible in many cases to cope with any variations which might exist, either in the sympathetic components or in the vascular channels in the operative area. Also, the extent of resection of the sympathetic fibers did not result in a complete ablation of the essential pathways.

Technique

For the reasons noted above and many other factors, I developed and began to utilize, in April, 1953, an anterior transthoracic transpleural approach through the third intercostal space. The incision extends from the parasternal line to the anterior axillary line and is carried through the skin, superficial fascia, and pectoralis major and intercostal muscles. The pleura is divided. In order to increase the size of the thoracotomy wound, the cartilage of the third rib is divided (Fig. 1). The lung is depressed downward to allow for complete and adequate exposure of the posterior chest wall from the fifth thoracic level up to the apex of the thoracic cage (Fig. 2*A*, *B*)

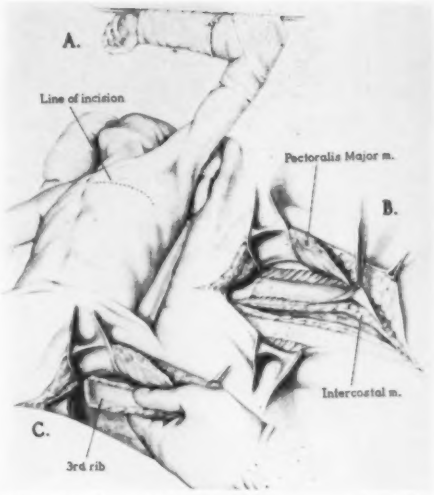


Fig. 1.—*A*, position of patient on operatnig table. The dotted line represents the location of the skin incision below the nipple. *B*, division of the pectoralis major and intercostal muscles in the third intercostal space. The parietal pleura is also divided in the same space. *C*, costal cartilage of the third rib anteriorly divided vertically by scalpel to increase the wound exposure.

Reproduced from article by author, published in A. M. A. ARCHIVES OF SURGERY, April, 1956, pp. 659-666, Fig. 3.

The parietal pleura is divided in a vertical manner over the angles of the ribs from the fifth thoracic level to the upper border of the first rib. This exposes the sympathetic chain and associated ganglia (Fig. 2*C*). By means of specially designed instruments, the dissection and resection of the chain can be expedited. The sympathetic chain is elevated and dissected free from the ribs and associated structures. The

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

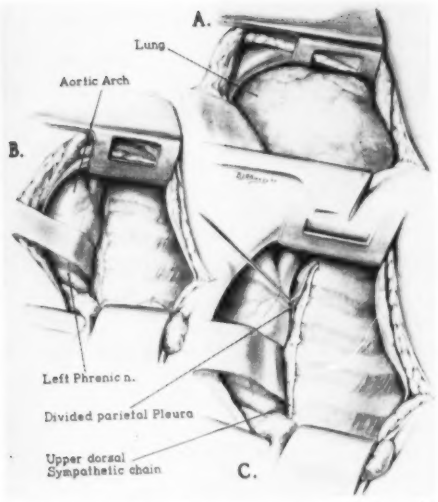


Fig. 2.—*A*, general exposure obtained after insertion of self-retaining chest retractor. *B*, special lung and cardiac retractors in place, revealing the upper posterior wall of the left thorax. The sympathetic chain and associated ganglia are readily seen beneath the posterior parietal pleura. *C*, the parietal pleura divided vertically over the sympathetic chain from the apex of the thorax to a point below the fifth rib. The medial branches, the ganglia, and the associated rami communicantes are easily visualized. Special long-handled hooks used to pick up the pleura facilitate division of this structure.

Reproduced from article by author, published in A. M. A. ARCHIVES OF SURGERY, April, 1956, pp. 659-666, Fig. 4.

chain is transected inferior to the fifth thoracic ganglion. The dissection is carried cephalad, dividing the rami at each level just inferior to the adjoining rib angles. Care is taken to avoid tearing into the intercostal vessels at each level, where the rami communicantes are in close approximation.

The second thoracic ganglion is usually large and aids in indicating that the dissection is reaching the critical point. From this area, the dissection is carried out more meticulously as the visualization of the lower third of the stellate ganglion is made. The dissection is carried cephalad to the point of isolation and identification of the first thoracic ramus. This is found just inferior to the lower border of the first rib (Fig. 3*A*). The mobilization and dissection of the stellate ganglion, lower third, is limited to a point just cephalad to the first ramus. Elevation of the stellate ganglion away from the chest wall or a more cephalad exposure of the ganglion will result in the destruction of the pupillociliary pathways, producing a Horner's syndrome.

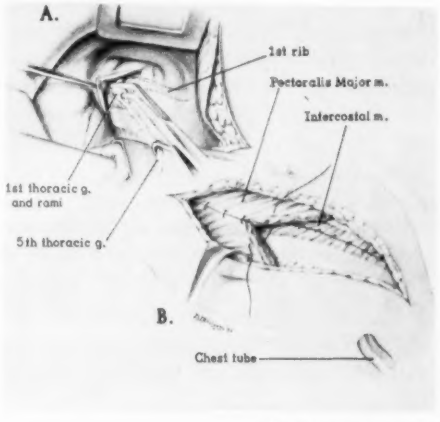
The first ramus is divided, and then the branch arising from the stellate ganglion just opposite the first ramus is likewise transected. Then, using the special right-angle scissors, the stellate ganglion (first thoracic ganglion), lower one-third, is transected just cephalad to the first thoracic ramus (Fig. 3*A*). The first to the fifth thoracic ganglia and the associated sympathetic chain is removed. This will result in ablation of all of the sympathetic pathways on this side, except in the occasional case when aberrant pathways or variations exist in the sympathetic system in this area.

The lung is then reexpanded, and the chest wall is closed in layers, using interrupted fine nonabsorbable surgical (silk) sutures (Fig. 3*B*). A chest tube is placed several interspaces below the incision. This is usually removed in 48 hours.

Fig. 3.—(*A*) The left upper thoracic sympathetic chain and five associated ganglia have been dissected free. The dissection of the stellate ganglion is carried just cephalad to the first dorsal ramus communicans, where it is transected by means of special right-angle scissors.

(*B*) The intercostal and pectoralis major muscles are separately sutured with interrupted 00 or 000 silk sutures. The intercostal chest tube is placed through a separate anterior stab wound, one or two interspaces below the intercostal incision.

Reproduced from article by author, published in the A. M. A. ARCHIVES OF SURGERY, April, 1956, pp. 659-666, Fig. 5.



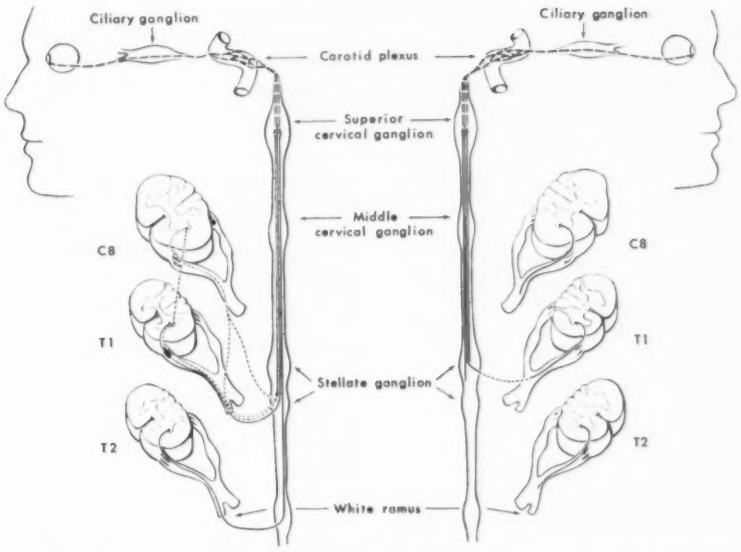


Fig. 4.—Pupillociliary pathways as recorded in the current literature and in texts are shown on the left side, with preganglionic neurons arising from the eighth cervical and first and/or second thoracic levels of the spinal cord. They pass via the first and second rami to enter the first thoracic ganglion.

The drawing on the right shows these pathways as our studies have indicated them to be. We postulate that the origin from the spinal cord is as recorded. However, these fibers leave the ventral roots and do not pass via the rami; they enter the upper portion of the stellate ganglion via a separate paravertebral pathway.

Pupillociliary Pathways

The current concepts concerning the sympathetic pathways which dilate the pupil in man, as recorded in the literature and texts, contend that the preganglionic neurons leave the spinal cord via ventral roots at the eighth cervical, and the first and/or second thoracic levels. These then pass via the first thoracic ramus communicans to enter the first thoracic ganglion (lower part of the stellate ganglion) (Fig. 4). These then ascend in the cervical sympathetic chain to synapse with postganglionic neurons in the superior cervical ganglion.

Therefore, according to authorities and investigators in this field, any surgical procedure which divides or removes the first thoracic ramus, the first thoracic ganglion, and/or the lower third of the stellate ganglion would result in a Horner's syndrome (miosis, enophthalmos, and drooping of the upper lid).

However, the division of the first thoracic and adjoining rami and the removal of the lower third of the stellate ganglion, as shown by our technique, does not result in a Horner's syndrome in 95% of the cases. From our clinical data and experience, we must assume that the sympathetic pupillociliary pathways in man do not traverse the first thoracic ramus to the lower part of the stellate ganglion. We contend that the origin of these pathways from the spinal cord is correctly recorded, but that the point of entrance to the stellate ganglion must be in the upper, rather than the lower, part (Fig. 4), and that these neurons reach the stellate ganglion by a separate paravertebral pathway.

This method and extent of resection has a wide clinical application, as noted in the Table. Since it is not the primary purpose of this presentation to discuss the clinical aspects, no elaboration on the various dis-

eases and conditions listed in the following Table will be made.

Indications for Upper Thoracic Sympathectomy

Angina pectoris—coronary heart disease
Peripheral arteriosclerosis
Raynaud's disease—acrocyanosis
Buerger's disease—scleroderma
Causalgia—Sudeck's atrophy
Frostbite—chilblains
Shoulder-hand syndrome—hyperhidrosis
Paroxysmal tachycardia—carotid sinus syndrome
Thrombosis of major vessels
Arteriovenous fistula and aneurysm
Phantom limb—erythromelalgia

Summary

The anterior transthoracic transpleural approach for upper thoracic sympathectomy provides an easier and better exposure than other techniques. It can be accomplished with a lower morbidity and mortality than former procedures. It has a wide clinical application and provides for a complete sympathetic denervation of the head, neck, shoulder, upper extremity, heart, and coronary circulation.

It incurs no physiologic changes which would interfere with the patient's socio-economic life.

It is a technique which avoids a Horner's syndrome, even though the lower part of the stellate ganglion is removed and the first thoracic ramus is divided. As a result of our technique and studies, a new concept concerning the sympathetic pupillociliary pathways in man is proposed.

Veterans' Administration Center (9).

DISCUSSION

DR. LOUIS T. PALUMBO, Des Moines, Iowa: [Slide] As you will recall, I indicated that this procedure had a broad clinical application. I have listed on this slide the conditions in which I think this operation is indicated. In most instances these patients can be considerably improved symptomatically and otherwise by this type of procedure.

[Slide] I mentioned the pathways to the eyes (Fig. 4). On your left are shown the pathways as described in the text and the literature, the preganglionic neurons coming from the first thoracic portion of the cord (the majority), passing by way of the first thoracic ramus into the first thoracic ganglion, and then up through the stellate ganglion to the eye. Therefore, according to previous investigators, any operation which divided this ramus or removed this portion of the stellate ganglion resulted in a permanent Horner's syndrome.

On the right side we have shown our concept of the pupillociliary sympathetic pathway. We think it comes out of the cord as previously described, but does not pass via the first thoracic ramus into the first thoracic ganglion, but apparently goes by some separate pathway to the upper portion of the stellate ganglion. As we have shown, we removed this portion of the stellate plus the division of the first ramus without producing a Horner's syndrome in 95% of the patients.

[Slide] This is an interesting case to help prove our point. These photographs were taken of the pupils in the same patient under the same photographic conditions, and you will note that the upper photographs were taken preoperatively before any blocks. The pupils are regular and equal.

The center photographs are shown here. After a left thoracic sympathectomy you see the pupils remain regular, and equal. You will note that the patient has sweating on the right side and no sweating on the left. I think you can see the perspiration here.

In the lower group of photographs on this slide of the same patient, the left stellate ganglion was blocked one month after a left thoracic sympathectomy of the type described, and you see the patient has a miotic or small pupil; this indicates that the pupillociliary sympathetic pathways remained intact after an upper thoracic sympathectomy as described before, in which the lower third of the stellate ganglion was excised and the first thoracic ramus divided.

Homograft Patch Repair of Bullet Wounds of the Aorta

Experimental Study and Report of a Case

HAROLD E. KLEINERT, M.D., Louisville

Vascular injuries have received a vast amount of study during the past 15 years as a result of the abundant clinical material provided by two wars and an ever-increasing rate of civilian trauma. Most of the literature, from both war and civilian experience, deals with injuries to peripheral vessels. Very little has been written concerning wounds of the aorta. The obvious answer to the paucity of reported cases of aortic wounds is, of course, that patients with an injury to the aorta usually die of severe hemorrhage before medical care is obtained.

Admission of a patient to the Louisville General Hospital with a gunshot wound of the thoracic aorta, which was successfully repaired, provided the stimulus for an experimental study of aortic gunshot wounds.

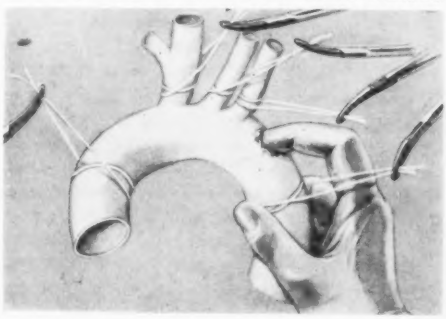
Report of Case

A 42-year-old Negro was admitted to the operating room at the Louisville General Hospital on Oct. 20, 1956, some 15 to 20 minutes after having been shot in the chest. No pulse or blood pressure could be obtained. His respirations were short and gasping, and involuntary defecation and urination had occurred. Unmatched O Rh-negative blood, available in the operating room for another patient, was started immediately through a No. 15-gauge needle. A pulse was noted after rapid infusion of 1 liter of blood.

Examination revealed a bullet wound in the left second intercostal space in the midclavicular line. No wound of exit was found. The chest x-ray revealed the bullet to be in the region of the right scapula. After oral endotracheal intubation, anesthesia with nitrous oxide and ether was begun. A thoracotomy through the left fourth intercostal space revealed the pleural cavity to contain approximately 2 liters of blood and clots. Exploration of a large upper mediastinal hematoma produced vigorous arterial bleeding, which was controlled with digital pressure. The aorta was dissected out, exposing a 1.5 cm. tangential wound on its posterior superior surface, 2 cm. distal to the left subclavian artery (Fig. 1). Following mobilization of the aorta, proximal and distal control was obtained by encircling the arch and its branches with umbilical tapes.

Blood flow was momentarily obstructed by tightening the tapes as the occluding finger was removed from the wound and the curved vascular clamp applied (Fig. 2). Lateral aortorrhaphy was accomplished with a double layer of continuous

Fig. 1.—Hemorrhage was controlled by digital occlusion during mobilization and looping of umbilical tapes around the aortic arch and its branches.



From the Department of Surgery, University of Louisville School of Medicine.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

Part of this work was done with the assistance of James S. Reiser, Student Research Scholar, supported by a grant from the Commonwealth Life & Accident Insurance Company.

The artery homografts used in this work were obtained from the University of Louisville Artery Bank, established and supported by grants from the Louisville, Ky. and Paducah-McCracken County Heart Associations.

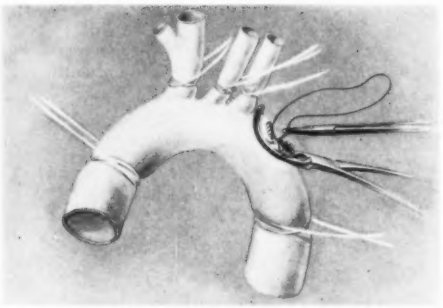


Fig. 2.—A vascular clamp was applied around the wound, as repair was accomplished with a running 0000 arterial silk suture.

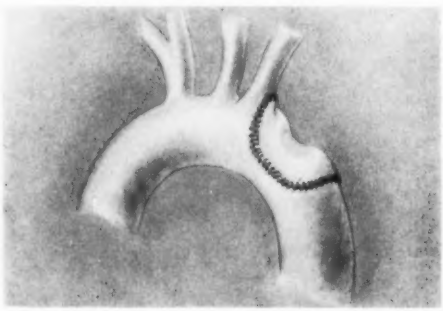


Fig. 3.—Appearance of the completed "patch."

0000 silk sutures. Four and one-half liters of blood was administered during the procedure. Upon completion of the operation his blood pressure was 120/88. Approximately 56 hours after admission he developed abdominal pain and signs of peritoneal irritation. Exploration under nitrous-oxide-oxygen-ether anesthesia supplemented with succinylcholine chloride U. S. P. revealed a 3 cm. contused and questionably viable area on the anterior surface of the cecum. A cecostomy was performed because of the danger of perforation.

On the fourth hospital day, thoracotomy was again performed to examine the site of aortic repair. The repair appeared intact, with no apparent weakness or evidence of necrosis. There was some resulting stricture at the site of the repair, with consequent reduction of the lumen to three-fourths of its normal size. Careful palpation revealed no thrill. The injury was too close to the subclavian artery to permit replacement even had there been sufficient evidence of aortic damage to justfy this. A reconstituted freeze-dried aortic homograft tailored to form a patch was sutured over the site of repair for reinforcement with 0000 continuous arterial silk sutures (Fig. 3). The postoperative course following this third procedure was uneventful. The cecostomy closed spontaneously after removal of the tube. The patient was discharged from the hospital 20 days after admission.

One year after injury he remained well, and examination revealed the presence of all peripheral pulses. Blood pressure was equal in all extremities.

This man was reexplored on the fourth day because of doubts as to continuing viability of the aortic wall adjacent to the laceration produced by a high-velocity missile. His extremely critical condition forced us to use the simplest type of repair which would save his life. Reexploration revealed the repair to be intact.

Resection and replacement of any part of the thoracic aorta is a formidable procedure; it would have been even more so in this case because of proximity of the laceration to the subclavian artery. Therefore, the idea of homograft patch reinforcement was suggested and carried out. Subsequently, animal experimentation was done (1) to determine the extent and results of injury to the aortic wall in and adjacent to lacerations produced by high-velocity missiles and (2) to determine the efficacy of homograft "onlay" type of repair.

Previous Reports

Since the introduction of firearms there has been much speculation and investigation as to the mechanism of wounding. Factors considered include bullet heat, the influence of rotation produced by rifling, the "projection destructive effects" (including momentum), and the relationship between the sectional area of the bullet and the type of tissue through which it passes.[1] The effectiveness of some factors, such as bullet heat, was proved erroneous years ago.

Callender and French demonstrated the physical disturbance produced by a bullet traversing a medium to be of longer duration than the actual length of time the bullet was in the medium.[2] Harvey and his co-workers studied the effect of high-velocity missiles in tissue, in water, and in gelatin gel blocks.[3] They demonstrated the formation of a large temporary cavity which pulsated several times before subsiding, shock waves in tissue, a region of extravasated blood, and the

formation of a permanent cavity larger than the sectional area of the bullet. The effect of penetration of tissue by a high-velocity missile was likened to the effect of a small explosion in tissue. The same group of Princeton workers shot cats in the abdomen, again demonstrating that passage of a high-velocity missile has an explosive effect within tissue, producing severe damage some distance from the path of the missile.[4,5] Examination of arterial gunshot injuries has revealed intimal damage to extend beyond that expected from the appearance of the wound. Moore and his associates demonstrated microscopic intimal damage to extend 3 mm. beyond that apparent grossly.[6,7] In the Korean War, Jahnke and Howard carried debridement approximately 1 cm. into normal vessel beyond the point of gross intimal damage.[8]

Many fatal cases of aortic wounds, with survival several days in some, have been reported; however, there seems to be little value in recounting these here.[9-11]

The first successful repair of a wound of the aorta is attributed to Dschanelidze, who successfully repaired a 1 cm. stab wound of the ascending aorta within the pericardial sac.[12] In 1926 Wildegans reported the successful closure of a 1 cm. stab wound of the abdominal aorta.[13] Blalock, in 1934, reported a successful repair of an ice-pick wound of the intrapericardial portion of the ascending aorta.[14] Successful repair of stab wounds of the intrapericardial portion of the ascending aorta was reported by Elkin in 1941 and 1944.[15,16]

A successful closure of a 3 mm. shrapnel wound of the abdominal aorta was reported by Dubinskiy in 1944.[17]

Holzer reported two cases of gunshot wound of the abdominal aorta in 1948. The first patient was a 26-year-old Negro woman shot with a 32-caliber revolver, which produced a 5 mm. wound on the anterior surface of the aorta. Unable to do a primary closure, he inserted a Vitallium tube 5 mm. in diameter, tying it in place with large cotton tapes, thus excluding the injured portion of the aorta. She developed partial paralysis of the right foot and had diminished femoral pulses, with no recordable blood pressure in the legs. The patient otherwise was asymptomatic and able to walk long distances. The second patient was a 28-year-old white man shot with a 22-caliber rifle, producing a 1 cm. rent in the anterior surface of the aorta, presumably at the site of origin of an anomalous left gastric artery. The rent was grasped and approximated with Babcock forceps, and edges of the wound were repaired with 00000 silk. The postoperative course was uneventful.[18] In 1952 Beattie and Greer reported a case of a 21-year-old Negro man who had a 14 mm. laceration of the aorta within the pericardium and who survived. Cardiac tamponade developed slowly, and surgery was performed 48 hours after injury.[19] Moore and associates reported in 1954 a case of gunshot wound of the abdominal aorta in a 14-year-old girl, who died 23 days after surgery of disruption of the aortic repair.[6,7]

The literature contains reports of successful closures of at least five intrapericardial stab wounds of the ascending aorta,[12,14-16,19] one stab wound of the abdominal aorta,[13] one shrapnel wound of the abdominal aorta,[17] and two gunshot wounds of the abdominal aorta.[18] Several cases of successful closure of an aortic venous fistula are recorded in the literature.[20,21]

De Bakey and Amspacher,[22] Jahnke and Seeley,[23] and Moore and his associates [7] have recently emphasized the ideal objectives of therapy in acute arterial injuries: control of hemorrhage, replacement of blood volume, and restoration of blood flow through the injured vessel.

Experimental Study

Material and Method.—Mongrel dogs weighing from 19 to 42 lb. were used as experimental animals. Anesthesia was obtained with intravenous pentobarbital sodium. Respiration was maintained with a mechanical respirator attached to an endotracheal tube. A left thoracotomy, usually through the left fourth intercostal space, was employed to expose the aorta. A chest wall retractor was inserted, and the left lung was displaced.

All animals were shot with a 22-caliber rifle set 3 ft. from the dog and employing 22-caliber short cartridges, which have a muzzle velocity of 1125 ft/sec. The animal was placed in the supine position so that the bullet passed through the aorta and out through the back muscles. The rifle was aimed so as to produce tangential wounds of the aorta; however, wounds produced included tangential wounds, through-and-through wounds, and, in one instance, complete division of the aorta.

Control of hemorrhage in the experimental animal was no problem, since the chest was open when the aorta was shot. Vascular clamps were immediately applied to occlude flow through the injured portion of aorta.

After debridement of adventitia, the external diameters of the aortic wound were readily recognized by careful inspection. The internal surface of the aorta revealed cracks and fissures in the intima, often extending 5 mm. beyond the external appearance of the wound. Usually, intimal damage corresponded to that shown by careful inspection of the external wound of the vessel. Damaged media and intima were not debrided in order to determine whether they would heal or undergo necrosis and rupture. Repair of the aortic wound was accomplished with a continuous 00000 arterial silk suture. Care was taken to place the needle through both intact media and intima of the aorta. Normal aortic wall could be recognized by resistance encountered as the needle was passed. Intima offers more resistance to the needle than media; if the media only was intact, a needle was easily inserted. Gross wounds of the intima were repaired, even though overlying media appeared intact. Sutures placed through media only produced a defect through which abnormal bleeding occurred when the vascular clamps were released.

The lines of repair and reconstruction followed whatever course seemed to produce the least constriction of the lumen. Long irregular and stellate lacerations were difficult to repair and sometimes required Y- or X-shaped patterns. Constriction of the lumen sometimes was produced, occasionally down to one-half of the original diameter of the vessel.

Animals summarized in Table 1 had the aortic repair reinforced with a homograft patch. The homograft had previously been sterilized with ethylene oxide and lyophilized. Prior to use, it was reconstituted in saline for 30 minutes. The patch was tailored so as to extend 5 mm. beyond the margins of the repair. A continuous 00000 arterial silk suture was employed to fix the patch to the aortic wall (Fig. 4).

Five dogs listed in Table 2 were wounded in a similar manner with a 22-caliber rifle. Repair of the aorta was accomplished by simple aortorrhaphy without reinforcement with a homograft patch (Fig. 5).

The last two dogs in Table 2 were shot in the aorta through gelatin gel blocks to simulate passage of the missile through the chest wall before striking the aorta. These were also repaired by simple aortorrhaphy without graft.

Blood was replaced as indicated. Each dog received 300,000 units of procaine penicillin G daily for two days.

All dogs survived, and most of them were killed, at varying time intervals. A few of the animals will be followed for a period of two years to determine long-term results.

Results.—In all instances the repair remained intact. Some animals with constriction of the aortic lumen developed slight poststenotic dilatation immediately distal to the repair. Femoral pulses remained palpable in every case. There was no aneurys-

TABLE 1.—*Summary of 22-Caliber Gunshot Wounds of the Thoracic Aorta Treated with Repair and Homograft Patch Reinforcement*

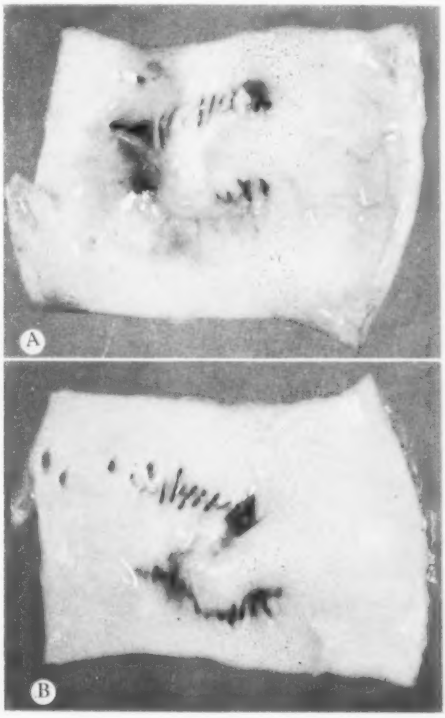
Dog No.	Date Shot	Date Killed	Description	Occlusion Time, Min.	Size of Graft	Femoral Pulses	Postmortem Findings
141	7/24/57	10/7/57	2.5 cm. tangential wound; region of 2d and 3d intercostal arteries	7	3.5×2 cm.	Present	Fibrosis and adhesions around graft site; proximal aorta 3.2 cm. circ.; repair 2.4 cm. circ.
33	8/1/57	9/21/57	1 cm. tangential wound between 2d and 3d intercostal arteries	5	1.5×1 cm.	Present	Adhesions about graft site; repair intact; proximal aorta 2.4 cm.circ.; repair 2.2 cm. circ.
31	8/26/57	10/25/57	2.5 cm., very irregular tangential wound; region of 2d and 3d intercostal arteries	20	3×2 cm.	Present	Adhesions, region of graft repair intact; proximal aorta 2.7 cm circ.; repair 2.3 cm. circ.
34	8/27/57	10/7/57	1 cm. tangential wound level of 1st intercostal artery	11	1×2 cm.	Present	Adhesions region graft; repair intact; proximal aorta 2.7 cm. circ.; repair 2.3 cm. circ.
3	7/11/57	Alive	Through-and-through wound 3 cm.; irregular; Y-shaped anteriorly; 8 mm. posteriorly; region of 2d and 3d intercostal arteries	15	3.5×3 cm., covering both wounds	Present but diminished	Alive and well
00	8/26/57	Alive	1.5 cm. tangential wound level 1st and 2d intercostal arteries	7	2.5×1.5 cm.	Present	Alive and well

TABLE 2.—*Summary of 22-Caliber Gunshot Wounds of Thoracic Aorta Treated by Simple Repair—No Patch Employed*

Dog No.	Date Shot	Date Killed	Description	Occlusion Time, Min.	Femoral Pulses	Postmortem Findings
149	8/14/57	10/23/57	2 cm. tangential irregular wound; level 2d and 3d intercostal arteries	16	Present	Few adhesions; intima smooth and intact; proximal aorta 2.7 cm. circ.; repair 2.4 cm. circ.
101	9/3/57	10/30/57	Aorta severed; edges irregular; level 2d and 3d intercostal arteries	15	Present	Few adhesions about repair; intima smooth and intact; proximal aorta 2.4 cm. circ.; repair 2.4 cm. circ.
105	9/4/57	10/28/57	Through-and-through irregular wound 2 cm. anteriorly; 8 mm. posteriorly between level of 1st and 2d intercostal arteries	14	Present	Minimal adhesions about repair; intima smooth and intact; proximal aorta 3.4 cm. circ.; repair 3.0 cm. circ.
109	9/6/57	9/25/57	1.8 cm. tangential wound level of 8th and 9th intercostal arteries; esophagus contused; hindquarter paralysis postop.	10	Present	Minimal adhesions about repair; intima smooth and intact; proximal aorta 2.3 cm.; repair 2.0 cm.; partial transection of spinal cord
140	8/30/57	Alive	Through-and-through irregular wound, 1.8 cm. anteriorly; 8 mm. posteriorly; level 2d and 3d intercostal arteries	19	Present	Alive and well
100	10/23/57	Alive	Shot through 2 in. gelatin gel block, 1 cm. tangential wound with 4 mm. tangential wound 3 mm. distal to first; level of 2d and 3d intercostal arteries	12	Present	Alive and well
151	10/28/57	Alive	Shot through 2 ½ in. gelatin gel block; tangential 1.2 cm. wound level 2d and 3d intercostal arteries	9	Present	Alive and well

Fig. 4 (Dog 141).—*A*, external appearance of homograft reinforcement of repaired bullet wound of thoracic aorta in dog killed 75 days after wounding. *B*, internal appearance of repair.

Fig. 5 (Dog 105).—*A*, external appearance of simple repair of through-and-through bullet wound of thoracic aorta in dog killed 54 days after wounding. *B*, internal appearance of repair.



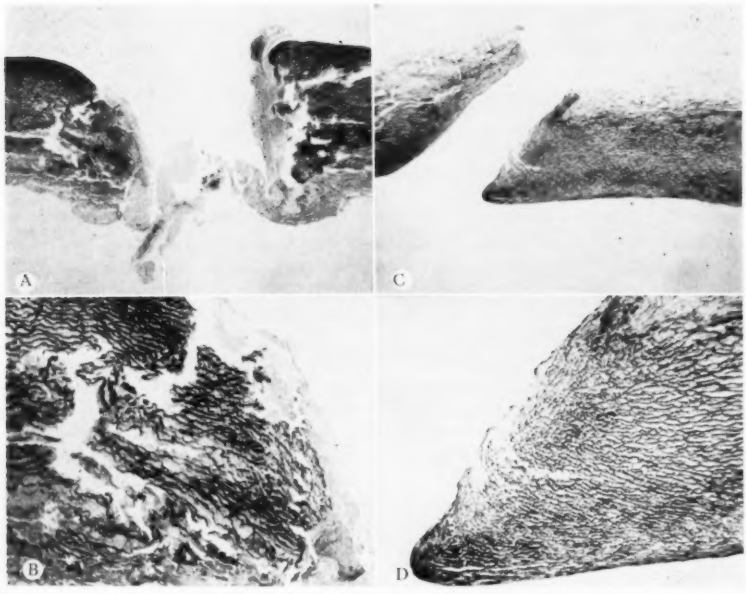


Fig. 6.—*A*, low-power view of fresh bullet wound of the aorta. There is longitudinal fragmentation of the media for a distance of 2 mm. *B*, high-power view of media demonstrating fragmentation. *C*, low-power appearance of fresh bullet wound of aorta shot through a gelatin block. There is clean disruption, with practically no fragmentation of the media. *D*, higher magnification, revealing practically no fragmentation of the media.

Fig. 7 (Dog 105).—Fibrous tissue, extending from a layer of fibrous tissue or adventitia, connects the disrupted media at the repair site. A suture can be seen in the left upper corner.

Figure 7

Fig. 8 (Dog 31).—Fibrous tissue bridges the gap between the aorta and the graft. The graft has retained its fibers intact.

Figure 8

mal dilatation. Thrombosis was not encountered. The intima appeared to be intact except where sutures protruded into the lumen. Through-and-through wounds of the aorta were more extensive on the anterior surface (point of bullet entrance) than on the posterior surface (point of bullet exit). Moore et al. believed more extensive wounds were produced when the aorta was exposed to air, since there was little or no opposing force to equalize tension from within the aorta.[7] The posterior surface of the aorta and aorta covered with a gelatin gel block have opposing forces; hence the wounds are smaller.

Histologic study of the aortic specimens showed significant variation only in the extent of injury to the arterial media. A fresh

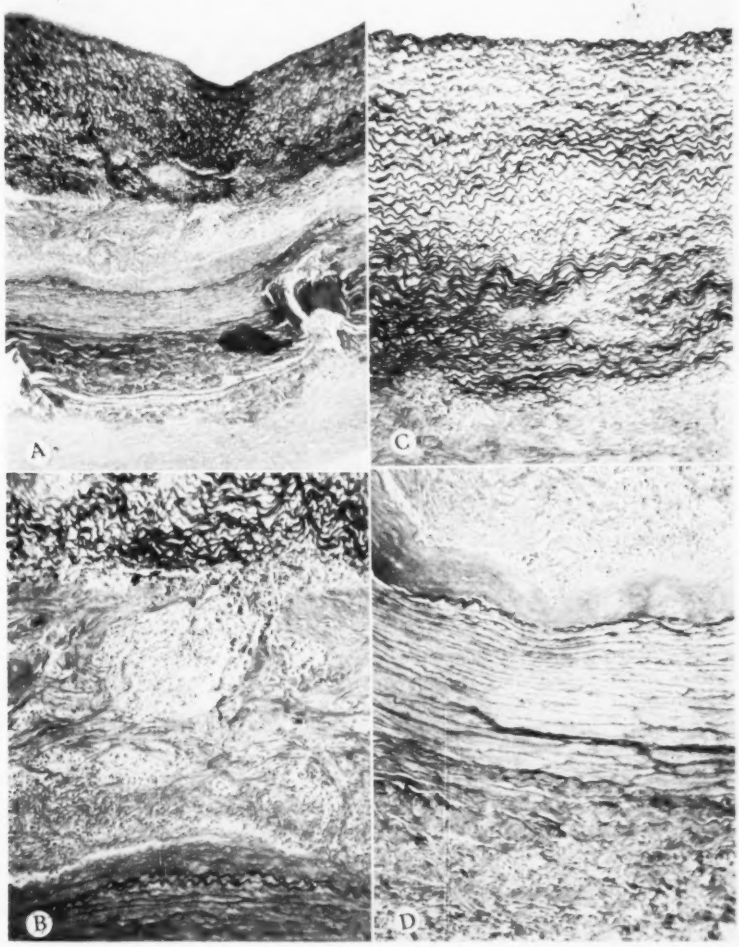


Fig. 9.—*A*, low-power photomicrograph of homograft patch. There is marked degeneration of elastic fibers of the graft. The space between the graft and the aorta is approximately 4 mm. in width. Note suture material in graft. *B*, higher magnification, demonstrating combination of scar tissue and pyogenic granulation tissue between aorta with preserved elastic fibers and graft with degenerating elastic fibers. *C*, higher magnification. Note well-preserved elastic fibers of aorta. *D*, note degenerated elastic fibers of graft. There is evidence of moderately severe inflammation in the adventitia. (This probably accounts for early degeneration of the elastic fibers of the graft.)

wound by a bullet shot through air revealed fragmentation of the media extending 2 mm. beyond the edges of the laceration. When the bullet passed through gelatin before reaching the aorta, there was practically no fragmentation of the media (Fig. 6). Following simple repair of the aorta, there was only minimal fragmentation of the media, and fibrous tissue united disrupted edges of the media. This fibrous tissue appeared continuous with a layer of fibrous tissue or regenerated adventitia overlying the media.

Dog 109, killed 19 days after injury, had thinning of the media at the anastomotic site, with very little fibrous tissue bridging the repair site.

Animals with homograft reinforcement developed more adhesions and fibrosis at the repair site than those treated by simple suture. The disrupted edges of the media were again found to be united by fibrous tissue (Fig. 7). The area between the repaired wound of the aorta and the overlying homograft patch was also bridged by fibrous tissue (Fig. 8). Elastic fibers of the homograft remained fairly intact except in Dog 34, killed 41 days after injury. In this animal there was marked degeneration of the elastic fibers with a space approximately 4 mm. in width between the repaired aorta and the graft; this was filled with a combination of scar and pyogenic granulation tissue. (Unusually rapid degeneration of the elastic fibers of the graft in this case is attributed to associated infection [Fig. 9].)

Comment

Extensive damage to the thoracic aorta could theoretically be treated by simple repair, by resection and end-to-end anastomosis, or by insertion of a vascular graft.

Since all of our experimental bullet wounds of the aorta repaired with simple suture healed satisfactorily without evidence of leakage or aneurysmal dilatation, homograft replacement or patch reinforcement appears unnecessary. Fibrous tissue does bridge the space between the graft and the repaired aorta. It should not be necessary to emphasize that debridement of excessively fragmented tissue would make the repair more satisfactory than in our experiments, since wound edges will be more readily recognized and approximated. Such debridement would also avoid faulty or only partial approximation of the layers of the aorta.

A wound of the thoracic aorta must be repaired as rapidly as possible, since occlusion for more than 20 or 30 minutes may be followed by severe sequelae, such as paraplegia.[24,25] Resection of much of the thoracic aorta would necessitate insertion of a vascular graft, and this might well increase aortic occlusion time to a dangerous point. The critical condition of the patient ordinarily would not permit more prolonged procedures, such as insertion of a vascular by-pass prosthesis or institution of hypothermia. In no instance did our 22-caliber bullets so severely lacerate the aorta that a vascular graft had to be resorted to. These considerations lend weight to arguments for simple closure, as discussed in the previous paragraph.

A homograft patch apparently does add some support to the repair, and this is probably worth remembering if the surgeon is not satisfied with the adequacy of his repair of a bullet wound of the aorta.

Summary

A case of successful repair of a gunshot wound of the thoracic aorta is presented.

Twenty-two caliber bullet wounds of the aorta were produced experimentally in dogs. Repair was accomplished by (1) aortorrhaphy alone and (2) aortorrhaphy with homograft reinforcement of the repair. The gross and microscopic appearances of the aorta following such treatment is shown.

Management of wounds of the aorta is discussed.

Conclusions

1. The external diameters of a bullet wound of the aorta can be determined following removal of the overlying adventitia.

Intimal damage, as viewed grossly on the internal surface of the aorta, does not extend more than 5 mm. beyond the margins of the external wound.

2. Damaged media and intima, when accurately approximated, heal without complications, such as hemorrhage, aneurysmal dilatation, or thrombosis.

3. In all instances wounds repaired by simple aortorrhaphy remained intact; therefore homograft patch reinforcement of the aortic wound should not be necessary.

4. If there is doubt as to the adequacy of repair of a bullet wound of the aorta, a homograft patch appears to strengthen the repair. Grossly there is increased scarring at the repair site, and microscopically fibrous tissue bridges the defect between the aorta and the graft.

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DISCUSSION

DR. JOHN L. KEELEY, Chicago: We would all like to congratulate Dr. Kleinert on his ingenious investigation.

I am sure that the reasonable belief that aortic wounds are rapidly fatal, due to exsanguinating hemorrhage, applies in almost all cases. There are, however, probably a dozen recorded exceptions. The author has presented one, and I should like to present what I believe is another instance in this category.

A 32-year-old man sustained two bullet wounds on his right side at close range. He must have had his right hand at his side, for one of the bullets passed through the soft tissue of his upper arm, just behind the midpoint of his humerus, and entered his chest through the right fifth intercostal space at the posterior axillary line. Apparently, it was deflected inferiorly by contact with a rib. The other bullet entered the region of the right hip and upper thigh.

Being unarmed, he thought it was a good idea to leave; he immediately experienced pain in his left groin, and his left leg buckled under him. About an hour later he was seen in the accident room. He had complete motor and sensory paralysis of his left leg. This was thought to be a neurosurgical situation. It was some time before the general surgeon saw him and concluded that his problem was one of massive ischemia.

In the meantime he had had an x-ray of his chest, which failed to show the expected missile, but an x-ray of his pelvis showed two of them.

[Slide] This is a postoperative photograph. I can assure you, however, that this missile on the right side was not causing him any trouble. The missile, indicated by this ink spot overlying the head of the femur, obstructed his left femoral artery. An embolectomy was done, but, because of the delay, he lost a portion of that extremity.

[Slide] This slide shows the missile being removed at the time of embolectomy.

We tried to determine some way of proving the site of entrance into the vascular system. We have not been able to do it. From the facts that he had a serosanguineous collection in the right thorax and some widening of the lower mediastinum, no pericardial effusion or pericardial friction rub, and no electrocardiographic disturbance, and considering the path of this missile, we concluded that it entered the lower part of the thoracic aorta. We believe that the widening of the mediastinum at that level was due to a para-aortic hematoma, which gradually subsided. In the two years we were able to follow this patient there had been no evidence of any aneurysmal dilatation, and he is now lost to follow-up.

I think it would be worth while on a long-term basis if Dr. Kleinert and his associates could report to us again on this very interesting case, and also on the future of the site of repair in their experimental animals.

DR. HAROLD E. KLEINERT, Louisville, Ky.: Needless to say, Dr. Keeley had a most unusual case. He told me about this yesterday, and I lost considerable sleep wondering how the bullet got in the aorta.

As I reviewed some of the literature, I came across case reports in which people had survived as long as 70 days with an unrecognized aortic wound. Certainly, it is possible for a bullet wound of the aorta to ocur and perhaps not be recognized.

Dr. Keeley, we plan to do a long-term follow-up. Unfortunately, our patient is now in a tuberculosis hospital. He had tuberculosis before he was shot; he went along all right for about twelve months, and then the tuberculosis became reactivated.

We plan to follow our dogs. We shall follow some of them up to two years.

The site of injury was in the thoracic aorta, usually in the area of the first to the third or fourth intercostal arteries.

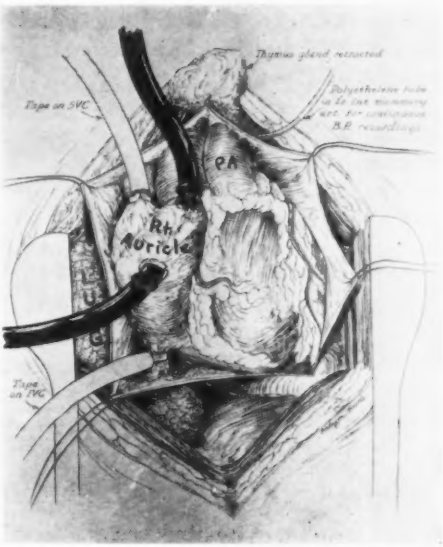
Median Sternotomy for Open Cardiac Surgery During Total Heart-Lung By-Pass

FRANK GERBODE, M.D.; MARK V. BRAIMBRIDGE, M.B., B.Ch., and DENIS G. MELROSE, M.B., B.Ch.,
San Francisco

The complexity of operation upon the heart and great vessels and the difficulties of physiological postoperative management make it desirable to have an operative exposure which is simple, rapid, and least disturbing to respiration. Having employed the median sternotomy in over 30 patients requiring total heart-lung by-pass, we are convinced that it has advantages over bilateral thoracotomy. It is the purpose of this paper to advocate its use for most intracardiac procedures.

Milton [1] was among the first to suggest median sternotomy, and those interested in the subject would profit by reading his excellent paper. It was also recommended by Lilienthal,[2] Roberts and Wilson,[3] and, more latterly, Holman, for pericardiectomy [4]; Shumacker, for pulmonary stenosis,[5] and Julian, for various intracardiac procedures.[6]

Initially we used the conventional transverse incision through the fourth interspace on the right and the third interspace on the left, with a V-shaped transection of the sternum. This gave excellent exposure of the heart and mediastinum but took more time to complete than we thought desirable in many of the more seriously ill patients. We often had the impression that the incision was more shock-provoking than the cardiac procedure itself. Similarly, the distortion and stretching of the mediastinal structures caused by retracting the thorax were not tolerated too well. Closure of the large transverse wound was also time-consuming.



View of exposure gained through the median sternotomy. The caval cannulae can be retracted with ease to gain full access to the aorta or to the various portions of the open right atrium. The femoral artery is used for return of the arterialized blood.

During the postoperative period respiration was often labored, and deep breathing and coughing were hard for most patients because of pain. Despite careful attention to the sealing of both sternal ends with bone wax, in two instances they continued to weep postoperatively, causing serum collections which required drainage.

Our experience in using median sternotomy in operations for pericardiectomy and in patients who were operated upon for pulmonic and aortic stenosis led us to believe it

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From the Department of Surgery, Stanford University School of Medicine.

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would be equally suitable for intracardiac procedures done on heart-lung by-pass.

Accessibility of all the important structures of the heart and great vessels is attainable through the median sternotomy (Figure), but it must be admitted that exposure of the ductus arteriosus is difficult and requires retraction and elevation of the mediastinum to the right. In fact, in one instance it was necessary to make a lateral intercostal incision in the third interspace to obliterate a large ductus encountered unexpectedly. Exposure and control of a persistent left superior vena cava is very easily accomplished by retracting the left atrial appendage downward. It required little dissection before a tape can be passed around it.

Since cannulation of the femoral artery is our standard procedure for return of arterial blood from the heart-lung machine, we have no experience of cannulation of the subclavian artery through this incision.

The following congenital defects have been operated upon successfully through the approach: (1) pulmonary stenosis, valvular and infundibular; (2) aortic stenosis; (3) tetralogy of Fallot; (4) interventricular septal defect; (5) interatrial septal defect; (6) total anomalous venous return from the right lung, and (7) left ventricular-right atrial defect.

Technique

The skin incision extends from just below the suprasternal notch to about 6 cm. below the xiphisternum. It is usually not necessary to remove the latter, and the abdominal cavity is not entered. The sternal periosteum is elevated a little on each side of the midline to create a cuff for subsequent closure. The attachment of the diaphragm to the sternum is separated with the index finger; then the mediastinal tissues are separated from the sternum by passing a curved malleable blade from the epigastrium to the suprasternal notch. It is not necessary to incise the tissues here, for one can feel the end of the blade. While an assistant holds the blade in place to protect the heart, a Stryker saw is used to cut through the entire length of the sternum. Bone wax is applied where necessary. The electrocautery is very useful to control small vessels.

Using blunt dissection, the mediastinal tissues are separated from the posterior aspect of the sternum before inserting the retractor. It has become a custom to use the left internal mammary artery for continuous blood pressure determinations, by cannulating it with a small polyethylene tube. The integrity of the left pleural space, when it can be retained, is an obvious advantage to this incision. Suction drains are used in both pleural spaces during the operation so that an accurate account of blood loss can be obtained. They are replaced at the end of the procedure by the customary chest tubes, with a third one in the anterior mediastinum.

The thymus is elevated superiorly and held by several suture ligatures to the wound edges.

The pericardium is incised widely in such a manner as to permit holding the heart in its normal position with traction sutures. Both cavae are encircled intrapericardially with umbilical tapes. The rubber cuffs which are used to clamp the cavae are not applied until just before the cavae are cannulated, for the reason that their weight might interfere with venous return during this interval.

After the intracardiac procedure is completed, the caval catheters are removed, the atrium repaired, and the pericardium closed loosely, using the thymus to cover the upper portion. The suction drains are replaced with conventional ones, and the tube is removed from the internal mammary artery, which is then doubly ligated. Closure of the sternum in children is most easily accomplished with interrupted sutures of 0 braided nylon, which are passed through the lateral margins of the sternum with heavy curved cutting needles at about 2 cm. intervals. In adults it is necessary to drill

holes, particularly in the upper sternum and manubrium. Braided nylon was found to be much more reliable than silk; it is not necessary to use wire. Care must be taken to repair the diaphragm lest a hernia develop later. The fascial layers of the upper abdomen are carefully approximated with interrupted sutures. The periosteal layer is approximated with interrupted sutures, which frequently also engage the medial margin of the pectoralis major. These further support the bone ends and prevent motion.

In no instance has there been any difficulty with exposure, with the exception of patent ductus arteriosus. A cyanotic adult with a severe pectus excavatum required correction of the bony defect before it was possible to expose the heart. In this patient the cyanotic state had caused such an increase in vascularity to the sternum that considerable blood was lost during the procedure. However, a good clinical result was obtained from the combined operation of repair of the sternum and correction of the pulmonary stenosis.

The average postoperative blood loss was less in this group than in the previous series in which bilateral transverse thoracotomy was employed. The sternum healed firmly in all instances. Thus far the incidence of keloid formation has been no greater than that seen in conventional thoracotomy incisions.

Summary

In a series of 30 patients median sternotomy was used to expose the heart and great vessels during repair of a variety of congenital defects using total heart-lung bypass. Exposure was excellent except for associated patent ductus arteriosus. Postoperative respiratory management was more satisfactory than with transverse thoracotomy. There were no wound complications.

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DISCUSSION

DR. DENTON A. COOLEY, Houston, Texas: Although the authors believe that the median sternotomy is the preferred method of approach to open heart surgery, I believe that it should be used only in selected types of cases.

During the past two years my colleagues and I have been using a pump oxygenator for cardiopulmonary by-pass and have operated upon 275 patients. In about 90% of these patients a bilateral anterior transverse thoracotomy incision was used, usually entering the fourth intercostal spaces on each side. The majority of our patients have had congenital cardiac anomalies, and 110 had ventricular septal defects. In the patients less than 2 years of age with ventricular defects, the mortality has been 30%, whereas in patients more than 2 years of age the mortality was 7%.

A number of factors are responsible for this high operative risk in the infant patient, since many are critically ill, with evidence of congestive failure and recurrent pulmonary edema. Respiratory complications are frequent in these infants, and death may result from inability of the weakened, debilitated patient to obtain proper pulmonary ventilation. Perhaps a median sternotomy would have its greatest usefulness in these patients, and we have employed it in two infants.

Unfortunately, there are certain disadvantages to the median sternotomy which the authors did not discuss and which probably deserve mentioning. In atrial defects the exposure may be compromised by the sternotomy approach. This is particularly true of the low atrial defect with cleft mitral valve, in which a lateral approach is almost necessary to expose the defect. In some patients we have

used a transatrial approach to a ventricular septal defect in order to avoid an extensive ventriculotomy incision. This procedure would be difficult through a median sternotomy.

In my experience with median sternotomy for cardiac surgery, as the incision is opened and the sternum and ribs spread upward and outward, the wound becomes deeper and the heart becomes more difficult to reach. This is particularly true in large children or adults.

DR. HENRY SWAN, Denver: We have had experience with the transverse sternum-splitting bilateral incision for open heart procedures in approximately 250 patients, and, except on 3 occasions, we have not used the vertical sternotomy, as described here. One of the reasons why we have not felt too happy with use of this incision is that unless we deliberately went into the left pleural space and looked throughout the mediastinum, the problem of the presence or absence of a left superior vena cava would complicate tremendously any dry-heart procedure. We were trapped by that situation on one occasion. When one blandly opens the right auricle with the two vena cavae occluded, thinking everything is fine, and blood squirts out of the auricle in large amounts and continues to come, one becomes convinced of the importance of being sure that an aberrant left superior vena cava or an aberrant azygos vein on the left is not present.

I thought the exposure shown in the film today was extremely satisfactory, better than that we have been able to achieve. There is one other disadvantage, however, and that is that when you open the sternum and spread the chest laterally, the two halves of the sternum come up. Actually, it seems to us that the distance between one and the bottom of the wound increases, in contrast to the easy spread in the vertical direction. However, I noticed that the authors did put in chest tubes at least on the right; maybe they didn't show the picture of the left side. I suspect there was a tube on that side, too.

Therefore, one should not believe that the merit of the procedure is due to the unviolated integrity of the two pleural spaces; rather, if there is a better respiratory physiology, it is due to the lack of pain in the absence of an intercostal incision.

It has not been our impression that the patient cannot breathe well after a carefully closed bilateral transverse incision.

DR. DENIS MELROSE, San Francisco: I should like to add that there is another complication in which this incision does not help very much, and that is with the unrecognized patent ductus arteriosus. We have on one occasion been obliged to extend the incision into a transthoracotomy to ligate this.

We have been very impressed, however, with the difference in the postoperative breathing of these patients, and they complain of far less pain. I agree that there are some disadvantages to this incision, but hold that they are far outweighed by the advantages and do not hesitate to recommend median sternotomy.

Diagnostic Biopsy of the Pericardium and Myocardium

MILTON WEINBERG, M.D.; EGBERT H. FELL, M.D., and JOSHUA LYNFIELD, M.D., Chicago

Surgical biopsy has been of little interest to the cardiologist or the surgeon as a method of establishing diagnosis in diseases of the pericardium and myocardium. It is the purpose of this paper to call attention to these entities in which the patient may benefit from the cooperation of the internist and the surgeon, and to describe a technique by which many of the cases of pericarditis and myocarditis may be accurately diagnosed and treated. The following five case reports are presented to illustrate the lack of specificity of symptoms and findings which may make etiologic diagnosis in these cases very difficult and to emphasize the necessity for direct examination of the pathologic anatomy if treatment is to be effective.

Read at the 65th Annual Meeting of the Western Surgical Association, Salt Lake City, Nov. 22, 1957.

From the Departments of Surgery and Cardiophysiology of the Cook County Hospital and the Presbyterian Hospital.

Associated Research aided by grants from the Otho S. A. Sprague Heart Foundation, the Chicago Heart Association, and the Hektoen Institute for Medical Research.

Report of Cases

CASE 1.—A 29-year-old white woman was admitted to the Cook County Hospital with a massive pericardial effusion of undetermined etiology, and symptoms and findings of cardiac tamponade and congestive heart failure. Pericardiocentesis on repeated occasions yielded up to 800 cc. of straw-colored fluid, of which cultures and cytologic studies were negative. The findings of routine roentgenography, electrocardiography, and angiocardiography suggested only the presence of pericarditis or myocarditis with pericardial effusion. Relief of the symptoms of tamponade after pericardiocentesis was only temporary, and the fluid reaccumulated rapidly after each removal. Approximately eight weeks after admission to the hospital, pericardial and myocardial biopsy specimens were taken, under local anesthesia. Sections of the myocardium were normal, and cultures of the fluid and pericardium were negative. Microscopic examination of the pericardium revealed a striking perivascular inflammatory reaction consistent with the diagnosis of lupus erythematous (Fig. 1). This reaction involved almost all of the blood vessels of the pericardium, and there was no evidence of inflammation in the surrounding

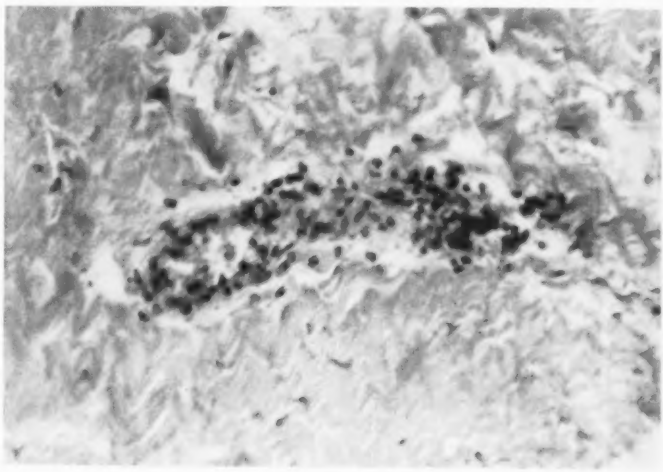

Fig. 1 (Case 1).—Photomicrograph of biopsy tissue from pericardium, showing perivascular inflammatory reaction consistent with diagnosis of lupus erythematosus. Hematoxylin and eosin stain.

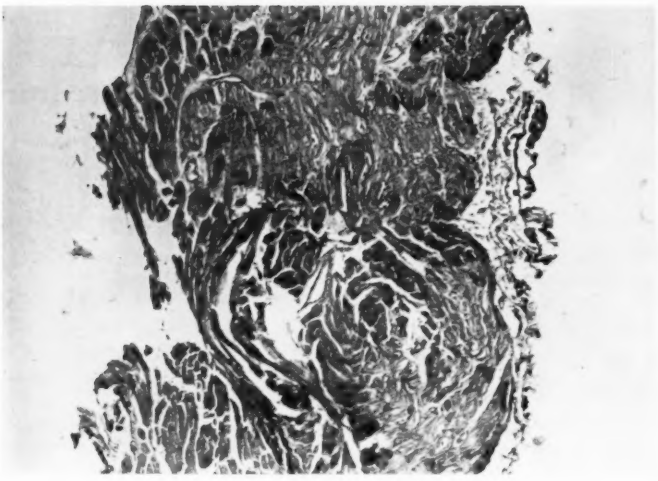

Fig. 2 (Case 2).—Photomicrograph of biopsy tissue from myocardium. Section demonstrates adequacy of specimen that may be obtained for examination. Hematoxylin and eosin stain.

tissues. The patient was treated with cortisone, with gradual regression of the pericardial fluid and symptomatic improvement during the following six months, after which she was lost to follow-up.

CASE 2.—A 51-year-old white man had been followed as an outpatient and with numerous hospital admissions over a period of seven years, with symptoms of exertional dyspnea and orthopnea. Physical findings of cardiac and liver enlargement, accompanied by increased venous pressure and ascites but no peripheral edema, suggested a diagnosis of constrictive pericarditis. The findings of extensive studies were of a nonspecific nature, including liver biopsy, which showed a granulomatous inflammatory reaction. Left- and right-heart catheterization studies demonstrated evidences of biventricular cardiac failure with marked elevation of atrial and ventricular diastolic pressures, consistent with a lesion constricting or infiltrating the myocardium. Biopsies of calf muscle and the gums were negative. Biopsy of the pericardium and myocardium was done under local anesthesia. The pericardium was free of adhesions and was normal grossly and microscopically. Sections of the myocardium showed a moderate degree of fibrosis consistent with the changes found in arteriosclerotic heart disease (Fig. 2). Special stains of the myocardial sections revealed no evidences of infiltration with amyloid. The elimination by biopsy of other suspected diagnosis in this patient makes a diagnosis of arteriosclerotic heart disease most likely.

CASE 3.—A 20-year-old Negro youth was admitted to the hospital with chills and fever and clinical findings suggestive of pericarditis or myocarditis. This patient was followed in the hospital over a period of four weeks, during which no definitive diagnosis was made despite extensive studies. Cultures of a small amount of serous fluid obtained by pericardiocentesis were negative for pyogenic bacteria and acid-fast organisms. The patient was treated with cortisone for 10 days, without improvement, and received streptomycin and aminosalicylic acid U. S. P., for several days on a presumptive diagnosis of tuberculous pericarditis. Surgical biopsy of the pericardium was done under local anesthesia. The pericardium was thickened and edematous, and the pericardial cavity was filled with fibrinopurulent exudate. Microscopic examination of the pericardium showed a granulomatous reaction with giant cells and tubercle formation, consistent with the diagnosis of tuberculous pericarditis (Fig. 3). This diagnosis was confirmed by cultures of sections of the pericardium. The patient was transferred to a sanatorium for specific antituberculosis therapy. Two months after the biopsy, pericardiectomy was performed because of signs of progressive pericardial constriction.

CASE 4.—A 33-year-old Negro man was admitted to the hospital with fever, chest pain, peripheral edema, dyspnea, and orthopnea of one week's duration. X-rays of the chest suggested the presence of pericardial effusion, but pericardiocentesis yielded only a few cubic centimeters of blood, which was thought to have come from the ventricle. In addition to extensive cardiac diagnostic procedures, this patient's hospital work-up included determination of the basal metabolic rate, radioactive iodine studies, muscle biopsy, 17-ketosteroid and hydroxysteroid determinations, x-rays of the skull, and bone-marrow preparation for lupus erythematosus. His treatment included courses of cortisone, corticotropin, potassium iodide, and

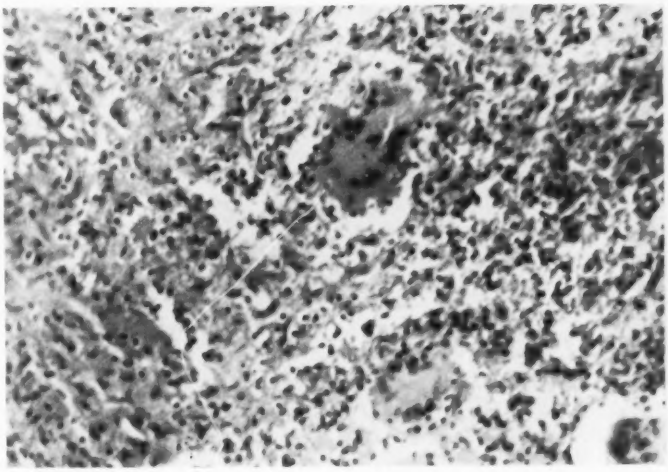

Fig. 3 (Case 3).—Photomicrograph of biopsy tissue from pericardium, showing granulomatous inflammatory reaction with Langhans type of giant cells. Cultures of pericardium confirmed diagnosis of tuberculous pericarditis. Hematoxylin and eosin stain.

streptomycin and isoniazid, in addition to penicillin and digitalis. Operation for pericardial biopsy revealed a pericardium filled with old blood, and sections of the pericardium showed only a nonspecific reaction to the presence of blood. On later questioning, the patient gave a history of an injury to the chest that occurred about the time of the onset of his symptoms, suggesting that the hemopericardium was traumatic in origin. This patient's symptoms subsided rapidly after removal of the blood, and he has been well since discharge from the hospital (Fig. 4).

CASE 5.—A 75-year-old white man was admitted to the hospital with a massive pericardial effusion and clinical findings of cardiac tamponade. Repeated pericardiocenteses yielded up to 1000 cc. of

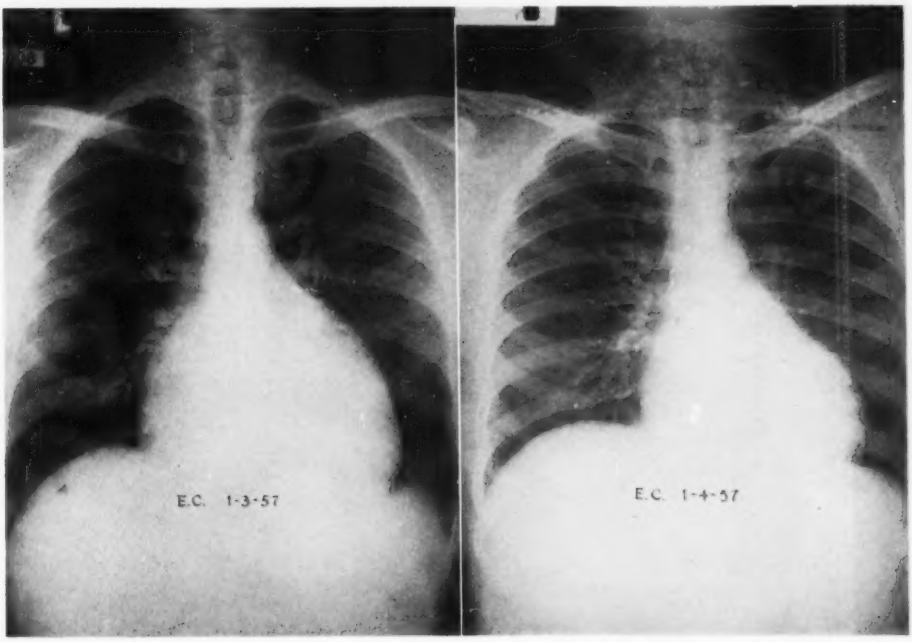

Fig. 4 (Case 4).—Left, preoperative x-ray of chest; right, x-ray of chest following drainage of hemopericardium, demonstrating reduction in size of cardiac silhouette.

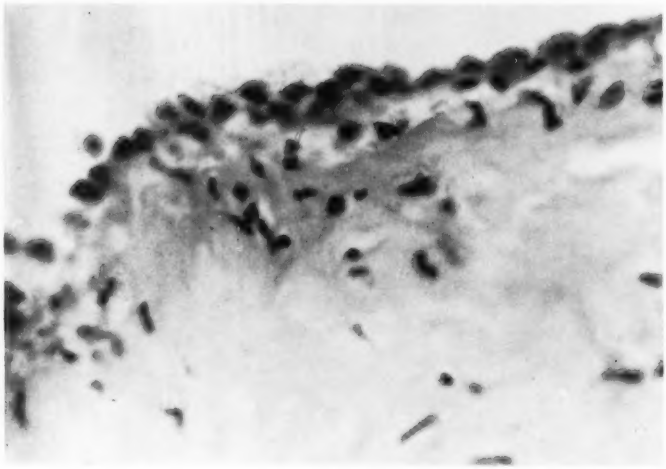

Fig. 5 (Case 5).—Photomicrograph of biopsy tissue from pericardium, demonstrating foam cells in the hyperplastic endothelial layer. Pericardial fluid in this case contained cholesterol crystals. Hematoxylin and eosin stain.

serous fluid, containing cholesterol crystals. Recurrence of the effusion after each aspiration was accompanied by return of the symptoms and findings of tamponade. Biopsy of the pericardium and myocardium was carried out under local anesthesia. In order to prevent the reaccumulation of fluid, a wide communication was established between the pericardium and the left pleural cavity. Myocardial biopsy was negative. Sections of the pericardium revealed a nonspecific inflammatory reaction with hyperplasia of the parietal epicardium (Fig. 5). Of particular interest in association with the cholesterol crystals found in the fluid is the presence of foam cells in the hyperplastic endothelium, similar to those found in arteries with early atherosclerosis. This patient was treated with cor-

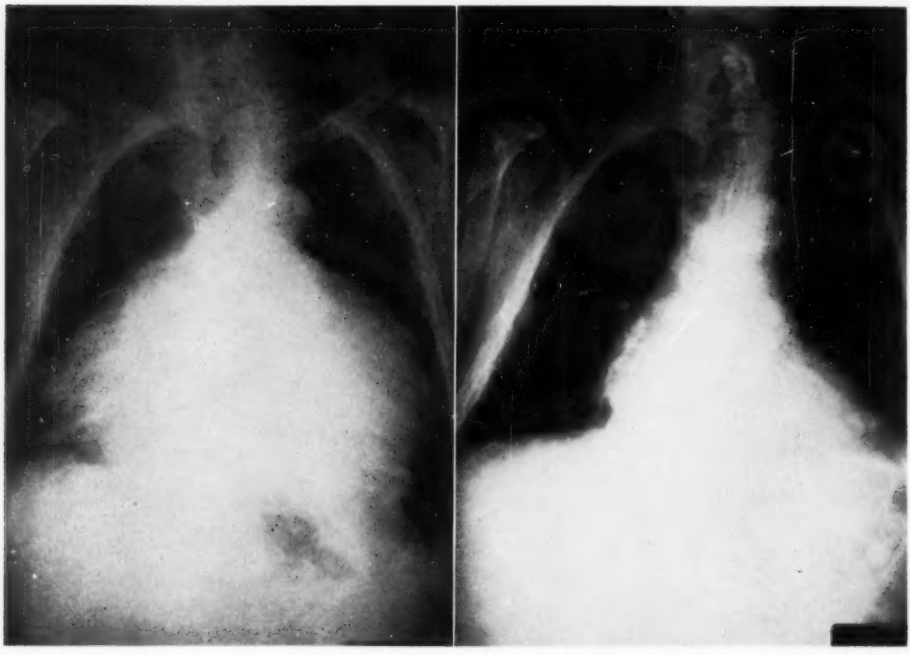

Fig. 6 (Case 5).—Left, preoperative x-ray of chest; right, x-ray of chest six months after biopsy and creation of pleuropericardial communication.

tisone on an empirical basis after operation, and, despite the fact that the etiology of the process is undetermined, the fluid has not reaccumulated and the patient is well at the time of this report. (Fig. 6).

Biopsy

Biopsy in each of these cases was carried out under local anesthesia, but with an anesthesiologist present and blood and endotracheal equipment immediately available. The incision was made over the fourth costal cartilage on the left. The cartilage was resected and its bed incised medial to the pleural reflection to expose the underlying pericardium. An ellipse of pericardium was taken for microscopic examination, and a second piece was taken for cultures. A section of myocardium was taken by undercutting a small area of heart muscle, in which a suture had been placed. The wound was closed in layers with silk sutures. There has been no postoperative morbidity other than minimal incisional pain. In the case in which the pleural cavity was deliberately entered, an intrapleural catheter was brought out of a lateral intercostal space and connected to underwater drainage for 24 hours to allow the escape of excess fluid. Oxygen was administered under positive pressure with a mask while the pleural cavity was opened to the outside and for a few minutes after the end of the procedure. In one other case in which the pleural cavity was entered inadvertently, the wound was closed about a catheter connected to underwater drainage while oxygen was administered with a mask. This catheter was removed before the patient left the operating room. X-rays of the chest after operation have shown the lungs to be well expanded in every case.

Comment

In 1954 Williams and Soutter [1] published a report of 17 cases of cardiac tamponade due to pericardial effusion, in several of which relief was obtained by surgical exploration and drainage externally or into the left pleural cavity. Their cases included patients with effusion due to carcinoma, tuberculosis, Pneumococcus infection, and nonspecific pericarditis. Silverstone,[2] in 1955, reported a case of nonspecific pericarditis in which relief from recurring tamponade was obtained by establishing a pleuropericardial communication. Proudfit and Effler,[3] discussing the diagnosis and treatment of pericarditis by pericardial biopsy, reported 16 cases in which this procedure was useful in establishing definitive diagnosis and specific therapy. These authors stressed the point that the recent development of therapeutic drugs and antibiotics has increased the importance of specific etiologic diagnosis in these cases. Attention should be called to the fact that pericarditis and myocarditis are by no means uncommon, and that they may be due to widely varied etiologic agents, including trauma, neoplasm, radiation, fungi, tubercle bacilli, pyogenic bacteria, and many other specific sources of disease. Biopsy, as described here, offers a means of differentiating and treating many of these entities with minimal risk to the patient.

Summary

The case histories of five patients are presented to demonstrate an operative technique for the accurate diagnosis, and in some cases the treatment, of diseases of the pericardium and myocardium. The surgical procedure is outlined, and a brief discussion is added to emphasize the necessity for accurate diagnosis if treatment is to be effective. It is apparent that surgical biopsy will add to our understanding of an important group of diseases about which much too little is known at present.

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Determination of the End-Diastolic Pressure Gradient Across the Mitral Valve at Mitral Commissurotomy

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The attempted quantitation of mitral valvular obstruction from data obtained by right-heart catheterization [1] has been extended and refined by techniques designed to record pressures directly from the left atrium and left ventricle [2-6] and by the use of simultaneous right- and left-heart catheterization and central arterial pulse forms for the estimation of flow and pressures in the cardiovascular system.[7-11] These procedures have made possible a reasonably accurate assessment of mitral-valve obstruction prior to surgery and have allowed an estimation of the degree of relief obtained by surgical intervention.[12,13] The recent reports of "restenosis" [14-20] raise the question whether these diagnostic adjuncts may not be of value in evaluating the surgical procedure itself.

This report concerns the application of the principles of left-heart catheterization to the operation of mitral commissurotomy, with a twofold purpose in mind: First, an accurate quantitation of the degree of mitral stenosis might be available at the time of surgery, especially in those patients in whom cardiac catheterization was not deemed necessary before surgery. Second, the adequacy of the surgical operation in reducing the obstructive gradient across the mitral valve can be assessed immediately and with objective precision. Through this means it seems likely that data might become available which should prove helpful in determining whether patients with symptomatic mitral stenosis after an apparently successful mitral commissurotomy are thus afflicted because of recurrent stenosis or because a residual gradient was left at the time of surgery.

Method

Left-heart catheterization is performed at the time of mitral commissurotomy by passing a cardiac catheter into the left atrium beside the surgeon's index finger. From here it is guided by the finger through the obstructed mitral orifice into the cavity of the left ventricle. Care is taken not to enlarge the orifice of the mitral valve before this initial pressure measurement has been made. This catheter is connected to a Statham P23D strain-gauge transducer, which is connected to a Sanborn direct writing recorder. Calibrations of pressure are made by a mercury manometer. After a satisfactory tracing of the left ventricular pressure is obtained, the catheter is withdrawn through the mitral valve into the left atrium. Continuous pressure tracings are recorded during this maneuver. The catheter is then removed from the heart, and the surgeon proceeds with mitral commissurotomy. After the commissurotomy has been performed, the procedure is repeated, with reintroduction of the catheter into the left ventricle and again into the left atrium. This process is repeated as many times as necessary until satisfactory obliteration of

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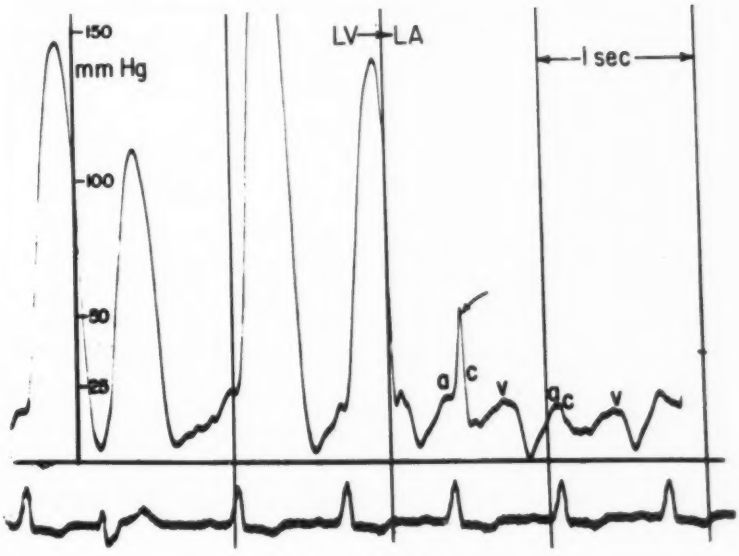

Fig. 1.—Normal LV-LA pressures.

the mitral diastolic gradient has been accomplished.

Material

Twenty-two patients have had measurements of the mitral diastolic pressure gradient before and after commissurotomy at the time of surgery. While this procedure was instituted only in occasional cases early in our series, it has now become a routine adjunct to the operation in the more recent cases. Twelve of these patients had a previous right- and left-heart catheterization as a diagnostic procedure prior to surgery.[7]

Results

1. A tracing is first shown for purposes of orientation in a patient without mitral stenosis, presenting a left ventricular pressure, normal left atrial pressure, and the normal pressure relations between atrium and ventricle in diastole. The diastolic pressures are equal in the two chambers (Fig. 1).

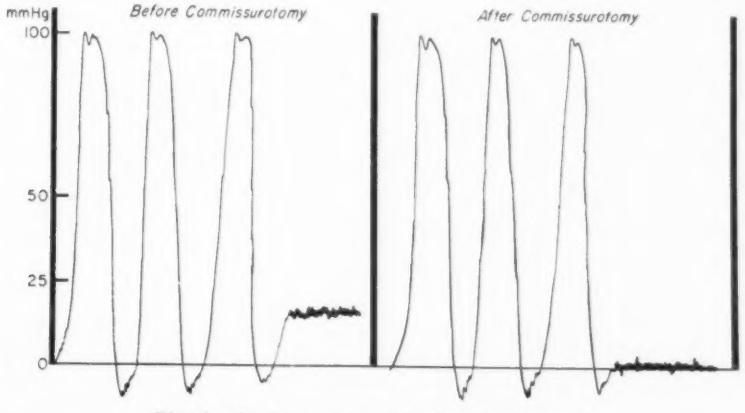

Fig. 2.—Gradients at surgery for mitral stenosis.

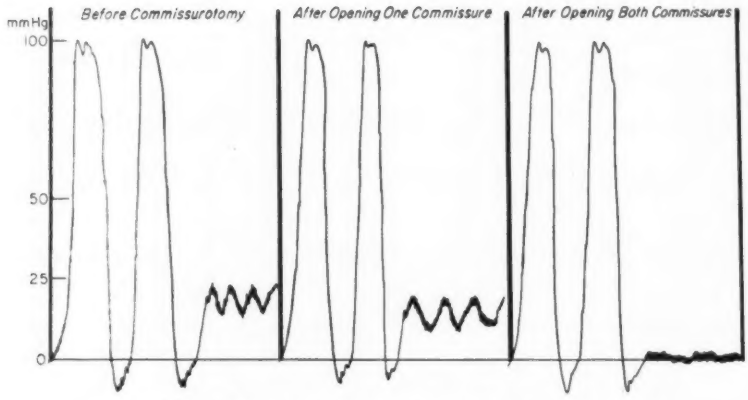

Fig. 3.—Gradients at surgery for mitral stenosis.

Figure 2 demonstrates the findings in a patient with mitral stenosis. Here the left ventricular pressure is 100/0 and the left atrial end-diastolic pressure is 15 mm. Hg. The second half of Figure 2 shows the tracing taken from the same patient after the mitral valve had been opened widely. The mitral end-diastolic pressure gradient has been abolished (Fig. 2).

Figure 3 shows the usefulness of this technique as a guide to more adequate surgery. The panel to the left shows a tracing on this patient with mitral stenosis prior to opening of the valve. The middle third of the Figure shows the tracing taken after a satisfactory split of one commissure had been accomplished. The orifice had been significantly widened, and it would have

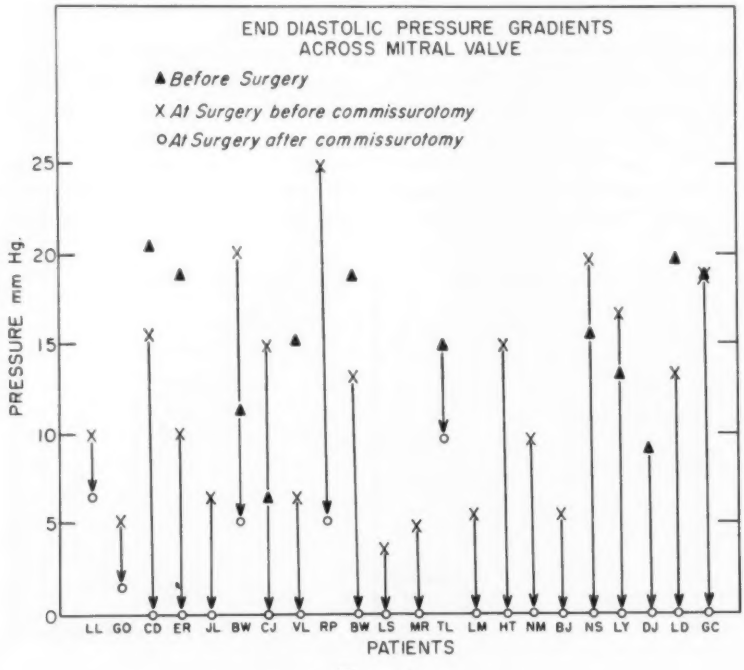

Figure 4

been a temptation to quit further manipulation; however, a pressure tracing at this point still indicated the existence of mitral stenosis. The third portion of this Figure shows the obliteration of the gradient after opening the second commissure and stripping the chordae tendineae and papillary muscles in the left ventricle.

Figure 4 is a graphic representation of the gradient measurements on the 22 patients in this series. In every case there has been a significant reduction in the obstructive gradient by mitral commissurotomy. In all but five instances the gradient has been completely abolished, and in many of these cases this has been possible only by serial determinations of the mitral diastolic gradient at the time of surgery. In five patients it was not possible to abolish the gradient completely, owing to valve rigidity and other factors, even though we were aware of some residual gradient. In each of these cases, however, there had been a significant reduction, associated with clinical improvement.

Comment

This information has added more precision to an otherwise blind surgical procedure and has helped in the performance of a more complete operation than would otherwise have been possible.

There are certain considerations in the interpretation of the measurements of these pressure gradients. The magnitude of the diastolic left atrial-left ventricular gradient is dependent not only upon the severity of the stenosis but also (1) upon the flow across the valve and (2) on the diastolic filling time, as determined by the heart rate. This accounts for the differences in gradient in the same patients under different conditions of preoperative left-heart catheterization, done under local anesthesia, and precommissurotomy determinations at surgery when the patient is under general anesthesia with an open thorax. Therefore, at least the assessment of the blood pressure and the heart rate at the time of measurements at surgery is necessary in order to understand more fully the meaning of the measurement of the gradient.

There have been occasions when it was evident that the gradient, after opening of one commissure, did not adequately reflect the improvement in the hemodynamic situation that seemed to have occurred. Occasionally, after opening of one commissure only, the flow is improved and the patient's peripheral arterial blood pressure rises. Under these circumstances of increased flow, the persistence of a gradient does not necessarily mean that the patient has not been improved. However, the obliteration of the mitral diastolic gradient associated with other signs of clinical improvement at the time of surgery has been our desired goal in these operations.

There is no question that only the simultaneous determination of blood flow across the mitral valve and the diastolic pressure differential between atrium and ventricle will provide sufficiently accurate information for a complete assessment of the surgical result. This, of course, is the purpose of four-chamber catheterizations before and after the surgical intervention.[7] We have confined the diagnostic procedures during surgery to the measurements of pressures only for several reasons: 1. It simplifies the procedure and makes it adaptable to almost any institution without the expense for elaborate equipment. 2. Unless the patient has been brought into a state of sharply reduced forward flow (shock), a reduction or obliteration of the end-diastolic pressure gradient must indicate relief of mechanical obstruction, irrespective of flow rates. The opening of the diseased valve is attended by an increased forward flow with shift of blood volume from the venous to the arterial side. If this were brought about without a change in valve area, the pressure differential would increase rather than decline. In consequence, the measurement of a pressure gradient alone, though not ideal, appears adequate for the purpose for which it was used.

The result of mitral commissurotomy depends not only on the skill of the surgical team but also on the character of the patient's valve. In this series we have not been able to obliterate the gradient entirely in five patients. These are patients who can be expected to have a less satisfactory result than others. Should they be examined in the future, the knowledge that the gradient was never abolished should be helpful in determining whether or not restenosis had occurred.

Conclusions

The determination of the left ventricular-left atrial pressure gradient has now become a routine part of the surgery for mitral stenosis in our hands, because it quantitates to some measure the degree of mitral stenosis and the degree of benefit to be expected from surgery. It has been most helpful to the operating surgeon to measure the gradient serially as stages of the valve surgery have been accomplished in order to do a more complete job. This should also provide a backlog of data to help answer in later years the question as to whether or not restenosis will occur after a satisfactory mitral commissurotomy. Analysis of the reduction of mitral diastolic gradients at the time of surgery has added additional evidence for effectiveness of mitral commissurotomy for mitral stenosis.

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Anatomy of the Esophageal Hiatus

Anatomic Studies on Two Hundred Four Fresh Cadavers

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The surgical treatment of esophageal hiatus hernia is essentially a development of the past 25 years, largely due to the contributions of Allison, Harrington, Tanner, Sweet, and others. The type of operation to be selected is in dispute, possibly because of lack of knowledge of the anatomy of the region involved and of the variations in that anatomy. In this connection, the muscular crura of the diaphragm about the hiatus are of considerable importance. This paper will discuss these muscular crura.

Descriptions of the relationships of the crura around the esophageal hiatus as given in textbooks and atlases of anatomy are often incomplete and sometimes incorrect. One of the first descriptions of a variation in the crura was by Low, in 1907. More recently, Collis, Satchwell, and Abrams [5] (1954); Collis, Kelly, and Wiley [4] (1954); Carey and Hollinshead [3] (1955), and Madden [9] (1956) have described these variations in greater detail.

Our study includes the variations in the muscular anatomy of the esophageal hiatus as found in 204 dissections done during the course of routine autopsy with the hiatal area left intact. The ages of the patients varied from newborn to 92 years, with the median age at 71.

The variations in the muscular arrangements of the crura about the esophageal hiatus can be divided into 11 types. In the listing that follows, after a brief description of the particular type, the number of cadavers in which the variation is found, and then the number of hernias found of that type will be given. In several instances hernias were grossly apparent; in others, whenever three or more fingers could be passed through the hiatus alongside the esophagus with the peritoneum intact they were considered hernias. As to the crura, it should be emphasized that the designations "right" and "left" crura are not related to the hiatus; they refer to whether that crus originates from the vertebrae to the right or the left side of the aorta.

Eleven Types of Arrangement of the Crura

Type I.—In this, the most frequent type, the right crus of the diaphragm contributes all the fibers which form the esophageal hiatus. The right margin is formed by a muscle bundle arising from the anterior aspect of the second to the fourth lumbar vertebrae and passing superiorly and anteriorly to insert in the central tendon. The left margin is formed by a muscle with similar origins to the above which passes posterior and superior to the right bundle, encircles the esophagus anteriorly, and inserts in the central tendon (Fig. 1) (100 cadavers; 12 hernias).

Type II.—This, the second most frequent type, is almost identical with Type I except that a slip of muscle arises from the left crus and passes posterior to the esophagus, inferior to the muscle forming the left margin, and inserts indefinitely into the posterior aspect of the muscle forming the right margin of the hiatus (Fig. 1) (64 cadavers; 5 hernias).

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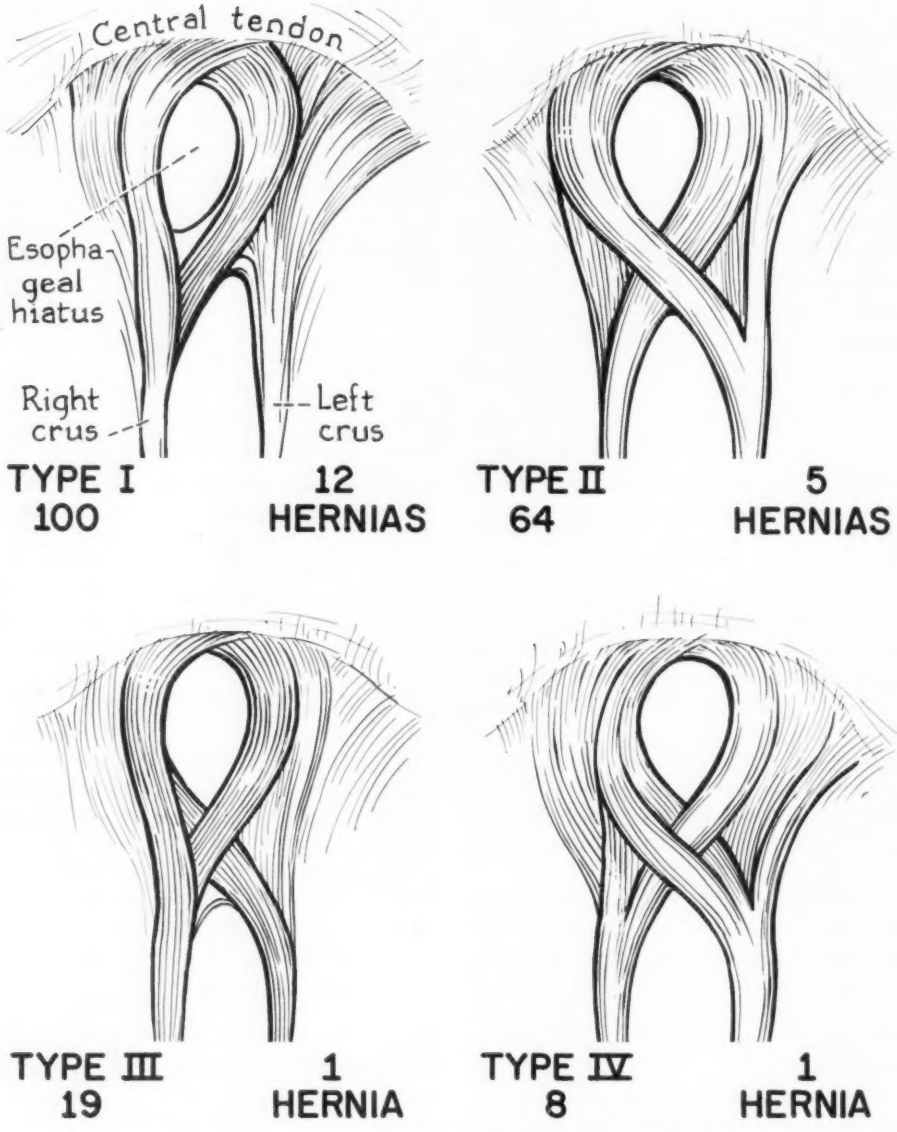

Fig. 1.—First four types of the arrangement of the diaphragmatic crura about the esophageal hiatus.

Type III.—This is also almost identical with Type I, but in this instance a small slip arises from the left crus, passes posterior and superior to the muscle forming the left hiatal margin, and inserts indefinitely into the muscle of the right margin. In both Types II and III these muscle slips are small, rarely over 1 cm. in greatest dimension (Fig. 1) (19 cadavers; 1 hernia).

(Types I, II, and III comprised 183 (90%) of the total 204 cases. At the same time, in these cadavers there were 18 hernias (86% of the total 21 hernias).

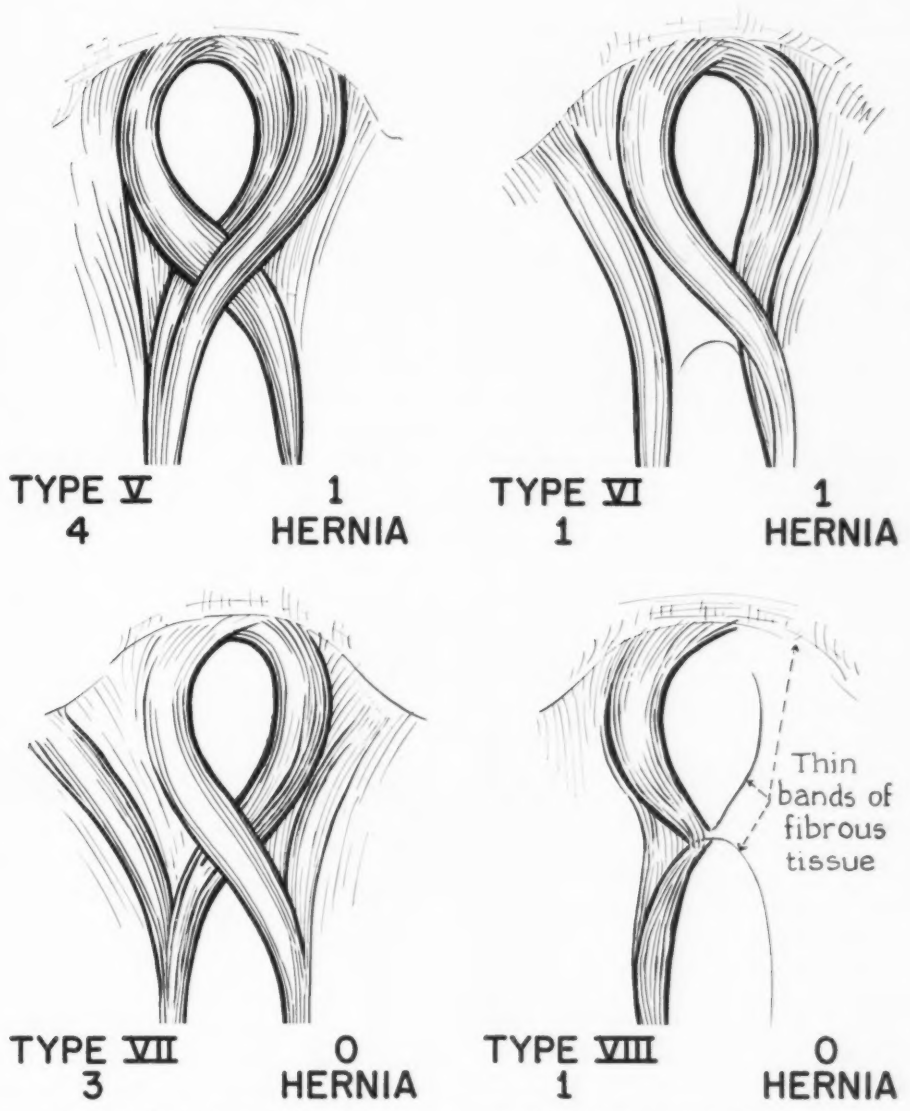

Fig. 2.—Types V to VIII of the arrangement of the diaphragmatic crura about the esophageal hiatus.

Some of Types IV to XI have not previously been described in the surgical literature. It is of interest to note that Collis found the muscle bundle which arises from the right crus to form the left margin of the hiatus to be innervated by a branch of the left phrenic nerve.)

Type IV.—Here the basic Type I is maintained, but two slips of muscle arise from the left crus, pass both inferior and superior to the fibers, and form the left margin and insert in the fibers of the right crus (Fig. 1) (eight cadavers; one hernia).

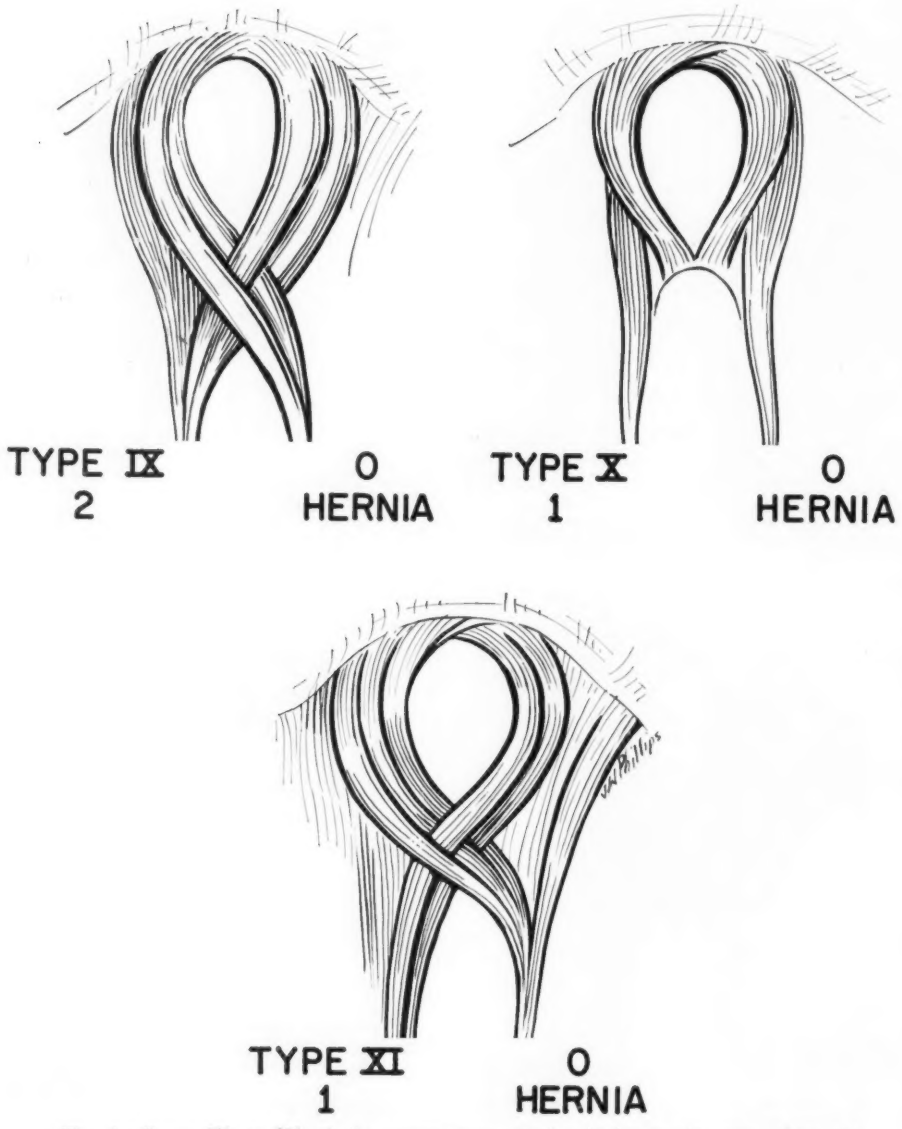

Fig. 3.—Types IX to XI of the arrangement of the diaphragmatic crura about the esophageal hiatus.

Type V.—In this variation the left margin of the hiatus is formed by two muscle bundles arising from the right; these are separated by a muscle slip arising on the left and passing to the right (Fig. 2) (four cadavers; one hernia).

Type VI.—This type is the opposite of Type I. Here all the muscle fibers of the hiatus originate from the left side (Fig. 2) (one cadaver; one hernia).

Type VII.—Here the hiatus is formed by muscle fibers originating from the con-

tralateral crura, with no fibers from the ipsilateral side contributing to the hiatus (Fig. 2) (three cadavers; no hernia).

Type VIII.—This represents an unusual instance of congenital absence of the left half of the diaphragm. Muscle fibers formed the right margin of the hiatus as diagrammed, but the left margin was made up of tough, fibrous tissue. There was no hernia (Fig. 2) (one cadaver; no hernia).

Type IX.—Here two muscle bundles arise from the right crus and pass to the left to form the left margin of the hiatus. Two slips also arise from the left crus, interdigitate with the above slips inferiorly, and intermingle with fibers from the right crus to form the right margin of the hiatus (Fig. 3) (two cadavers; no hernia).

Type X.—Here no fibers cross the midline of the hiatus; the margins are made up of muscle fibers originating from the ipsilateral crura and the arcuate ligament, as diagrammed. This arcuate ligament serves as a point of origin for muscle fibers in the above types, too, but there is considerable variation, and in many cases it is absent (Fig. 3) (one cadaver; no hernia).

Type XI.—Finally, in this type two slips arise from the right crus and pass to the left, interdigitating with three slips originating on the left. The right crus contributes some fibers to the right margin of the hiatus, but this is made up largely by the fibers from the left (Fig. 3) (one cadaver; no hernia).

Comment

The surgical treatment of esophageal hiatus hernia involves questions as to the thoracic (Sweet,[11] 1952, and others) or the abdominal (Lam and Kenney,[7] 1954; Harrington,[6] 1955; Beardsley,[2] 1956, and others) approach, as to whether the sutures in the crura should be placed in front of the esophagus (Tanner,[12] 1955; Sweet,[11] 1952, and others), behind the esophagus (Merendino, Varco, and Wangensteen,[10] 1949; Allison,[1] 1951, and others), both in front and behind the esophagus (Madden, 1956), or also lateral to the esophagus (Madden,[9] 1956). Our dissections indicate that sutures lateral to the esophagus may be necessary in certain cases, contrary to our previous opinion on this aspect of the subject. In certain cases the enlarged hiatal opening has a definite hockey-stick protrusion anteriorly and then to the left. None of the 11 types of crural arrangement seemed to be particularly prone to nor immune from hiatal hernia in our studies (except some of the rare types, of which the number of cases studied was insufficient for statistical analysis). While the paraesophageal hernias found in this series were few in number, in all cases the hernia was surrounded by the hiatus. In no instance did the hiatal muscles remain about the lower esophagus with the herniation presenting through the diaphragm to the right of the right hiatal margin, as some have depicted.

In the commoner types of arrangement of the crura, participation of the right crus in forming a border of the hiatus was greater than that of the left, but in the rarer types there was less difference in participation between the two crura.

Within each of the 11 types there may be considerable variation in the size of the muscle bundles involved. Observation of the muscle mass around the hiatus made it hard to visualize how there could be a hernia in a patient with strong muscles. At the same time, it seemed possible that a wasting of the muscles in later life could be a contributing factor to the development of hiatal hernias at such a time.

Some attention was paid to the phrenoesophageal membrane (ligament) during these dissections. In the bulk of them this structure was unsubstantial.

Summary

On the basis of dissections of 204 fresh cadavers, the variations in the muscular anatomy of the esophageal hiatus can be divided into 11 types.

Types, I, II, and III comprised 183 (90%) of the total 204 cases. Some of

Types IV to XI have not previously been described in the surgical literature.

In the majority of instances the significant muscles about the hiatus originate from the right side of the aorta, i. e., from the right crus.

Dept. of Surgery, University of Washington (5) (Dr. Harkins).

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DISCUSSION

DR. ROBERT SPENCER, Denver: Drs. Listerud and Harkins are to be congratulated on the excellence of their anatomic study. It is certainly done with a thoroughness that is characteristic of all the work that stems from Dr. Harkins' department.

The clinical importance of this study would seem to me to be the fact that all the variations which they encountered in these 204 dissections lend themselves pretty well to the conventional forms of repair for esophageal hiatus hernia. The one possible exception to this perhaps would be their Type VIII, in which there was attenuation of the left lateral margin of the hiatus.

Our interest in the anatomy of the esophageal hiatus distal to the esophagus stems from several recently encountered cases of lower esophageal, or so-called Schatzki, rings.

[Slide] These were described in 1953 by Dr. Richard Schatzki, of Brookline, Mass., and independently by Dr. Franz J. Ingelfinger, of Boston. They are usually, if not always, seen in conjunction with esophageal hiatus hernia. Many times they produce no symptoms, but about one quarter of them seem to produce intermittent dysphagia. Esophagogastric examination is always negative, in spite of the fact that on occasion in a few of these cases exploration has been done and a web resected. You can see at the lower end of the esophagus this symmetrical deformity, either at or just above the esophagogastric juncture, with a portion of the stomach lying above the diaphragm.

[Slide] This is a case in which the x-ray does not demonstrate diaphragmatic hernia but does show this lower esophageal ring. The patient was a 50-year-old man who complained of dysphagia on ingestion of solid foods. Esophagoscopic examination was negative. He had several dilations, without relief of his symptoms, and for that reason we did an exploration. We entered through the left chest and opened the esophagus about 4 or 5 cm. above the diaphragm, where this lesion is located. We were unable, to our chagrin, to demonstrate any lesion. We were able to pass a No. 30 catheter proximally toward the pharynx without meeting any form of obstruction, and distally, into the stomach. Therefore the esophagus was closed without a definitive repair.

[Slide] This is a postoperative x-ray of the same patient. He has been asymptomatic since the operation. We don't know what we did, but he is asymptomatic. In this slide the ring is no longer present. Presumably, the incision in the esophagus went through the area where the ring was located. There is a small defect which is a postoperative defect in the ower end of the esophagus.

I should like to ask Dr. Listerud and Dr. Harkins whether, in the course of their dissections, they encountered or made any observations which would shed light on the nature of the anatomic defect producing these rings.

DR. ARNOLD STEVENS, Beverly Hills, Calif.: This paper seems to me to be pertinent because of the increasing frequency of clinical repairs of hiatal hernia. This study affords a considerable amount of anatomical data which I am not aware of having previously been reported.

After hearing this report, I am convinced that many of us have based our hiatal hernia repairs too uniformly on the concept of the sole importance of the right crus of the diaphragm.

I believe Dr. Listerud and Dr. Harkins have shown that in some cases more attention should be paid to the left crus. Because of the anatomical variations they have demonstrated, it follows that the uniform use of the posterior repair only seems invalid. If recurrences are to be reduced, technique should be modified to fit the variations in anatomy encountered in each individual case. The results of this study should help us to do this.

Our personal clinical experience supports the finding that the phrenoesophageal ligament is usually unsubstantial. In some cases we do not even see it surgically.

DR. R. MORTON BOLMAN, Fort Wayne, Ind.: At the outset, I wish to commend Drs. Listerud and Harkins on their scholarly paper on the anatomy of the esophageal hiatus and thank them for inviting me to discuss it. In some academic quarters one hears rumors of the elimination of anatomy as a basic academic discipline, and it is said that anatomy should be "worked in with other subjects," rather than be taught as a discipline basic to all medicine, particularly surgery. It would be patently foolish for me to compete with the authors on this exact, anatomical, investigative ground. I shall therefore confine my few remarks to the clinical implications of their work, with perhaps a comment or two on my own experience with this entity.

First, I must own that Dr. Lloyd and I, and our associates, feel with Heneage Ogilvie, of England, that the diaphragm should not constitute a surgical "iron curtain." In no other entity, perhaps, is the barrier between thoracic and general surgery more obvious than in the correct treatment of hernia of the esophageal hiatus. We feel that this is no barrier, and we feel, further, that any surgeon who is not equally at home above and below the diaphragm should search his own soul before he undertakes hernial repair from either approach. It is quite natural that one should prefer, all things being equal, to approach this condition either from above or from below, but to limit one's self to either approach exclusively must necessarily on occasion have dire consequences for the patient. No less a man than Harrington achieved a recurrence rate as good as any with the approach almost exclusively from below, whereas many others have equaled it from above. We prefer to approach this condition from above with the plain understanding that should there be the slightest doubt of the abdominal presence of a pathological process as important as, or more so than, the hiatus hernia, then the approach should be from below. We agree that these hernias are easier to repair from above; but with an understanding of the midline incisions with removal of the xiphoid process, and even a median lower sternotomy when necessary, a very adequate and satisfactory exposure can be obtained from below. As a corollary of this attitude, it then becomes essential that any patient proved to have a symptomatic hiatus hernia must necessarily have a thorough investigation prior to surgery for the presence of gallstones, tumors, peptic ulceration, pancreatitis, vascular disease, mechanical obstruction, and, in the female, diseases of the uterus and adnexa. This presupposes the physical examination, as well as the ancillary x-rays and laboratory studies necessary to ascertain the presence or absence of the conditions mentioned.

Insofar as technique is concerned, excellent anesthesia has made it possible for the most ordinary of us to accomplish this procedure with maximum facility, minimal mortality and morbidity, and maximal chances for a successful long-term result. It remains then only that the operating surgeon must bring with him a thorough understanding of the anatomy, physiology, and embryology involved in this mechanical disease entity, and an alert awareness of those structural changes necessary to a physiological outcome.

In 9 out of 10 of these cases it is our custom to transpose the esophagus anterolaterally and repair the defect behind. Technically, we have found a tremendous advantage in the simple procedure of inserting those so important first two or three sutures with the left hand, using a long needle holder, while maintaining the exposure with the right hand and while keeping the spleen and celiac axis behind the right hand out of harm's way. We do not feel, in most instances, that any reinforcement of the diaphragm with autogenous material or foreign substances is necessary, because recurrences, in the vast majority of instances, result not from an inherently poor diaphragm but, rather, from an inherently poor repair. We have come to wonder about the word "recurrence." We have all frequently seen the "recurrent" inguinal hernia in which the hernia was in no way recurrent but, rather, was the original hernia buttressed for a short time by the plication of numerous layers of tissue in front of the untouched sac—a surgical house builded on the sands.

It becomes obvious, then, that the successful prosecution of the treatment of the esophageal hiatus hernia rests on a thorough understanding of the basic nature of the defect involved. The study by Dr. Listerud and Dr. Harkins has il-

lumined this area in a way helpful to us all. In short, it is the fine type of basic surgical research that we have come to expect of Dr. Harkins and his associates.

DR. W. P. KLEITSCH, Omaha: First of all, I should like to say a big "Amen" to Dr. Bolman's remarks, and I should like particularly to emphasize that one should differentiate between a postoperative persistence of hiatus hernia and a postoperative recurrence of hiatus hernia.

We always repeat the esophagogram and the upper gastrointestinal series before we discharge such a patient, and so we have a record of whether or not it is a persistence or a recurrence.

Second, I should like to protest against the use of the word "ligament" when one means phrenoesophageal membrane. Unfortunately, believe it or not (and I didn't bring along a slide to demonstrate this), if a histologic section of the phrenoesophageal membrane is stained for elastic fibers, one will find that it is composed of yellow elastic tissue. This, gentlemen, is not a ligament. A ligament is made up of collagenous fibers.

DR. MARK LISTERUD, Seattle: I should like to thank Dr. Bolman and Dr. Stevens for their remarks. We certainly feel as Dr. Bolman does about the repair—that we should be able to do it from either above or below.

In regard to Dr. Stevens' remarks about the posterior repair not always being adequate: If I may have your indulgence, I should like to show two more slides.

[Slide] Here is one of the hernias which I found. We see the defect here in the lower mediastinum and the tendinous portion of the diaphragm here. I have pulled down and out of this defect some of the transverse colon and about half of the stomach, but yet we see that the esophagus and the fundus of the stomach still lie within the defect.

[Slide] Here is the dissection in this case. This is a Type I hiatus. Note the elongation of the left margin of the hiatus. I would certainly concur with the writings of Harrington and Madden on this subject, that is, that a simple posterior repair of this hiatus very likely would be inadequate, and that placement of anteroposterior sutures in this area would very possibly be necessary to close this hiatus.

[Slide] Here is another hernia. This is not nearly as extensive as the one previously.

[Slide] Here is the dissection of this case. In this situation the hiatus has not been taken down, but it is actually in situ. Very likely a posterior repair here would be adequate to close this ring.

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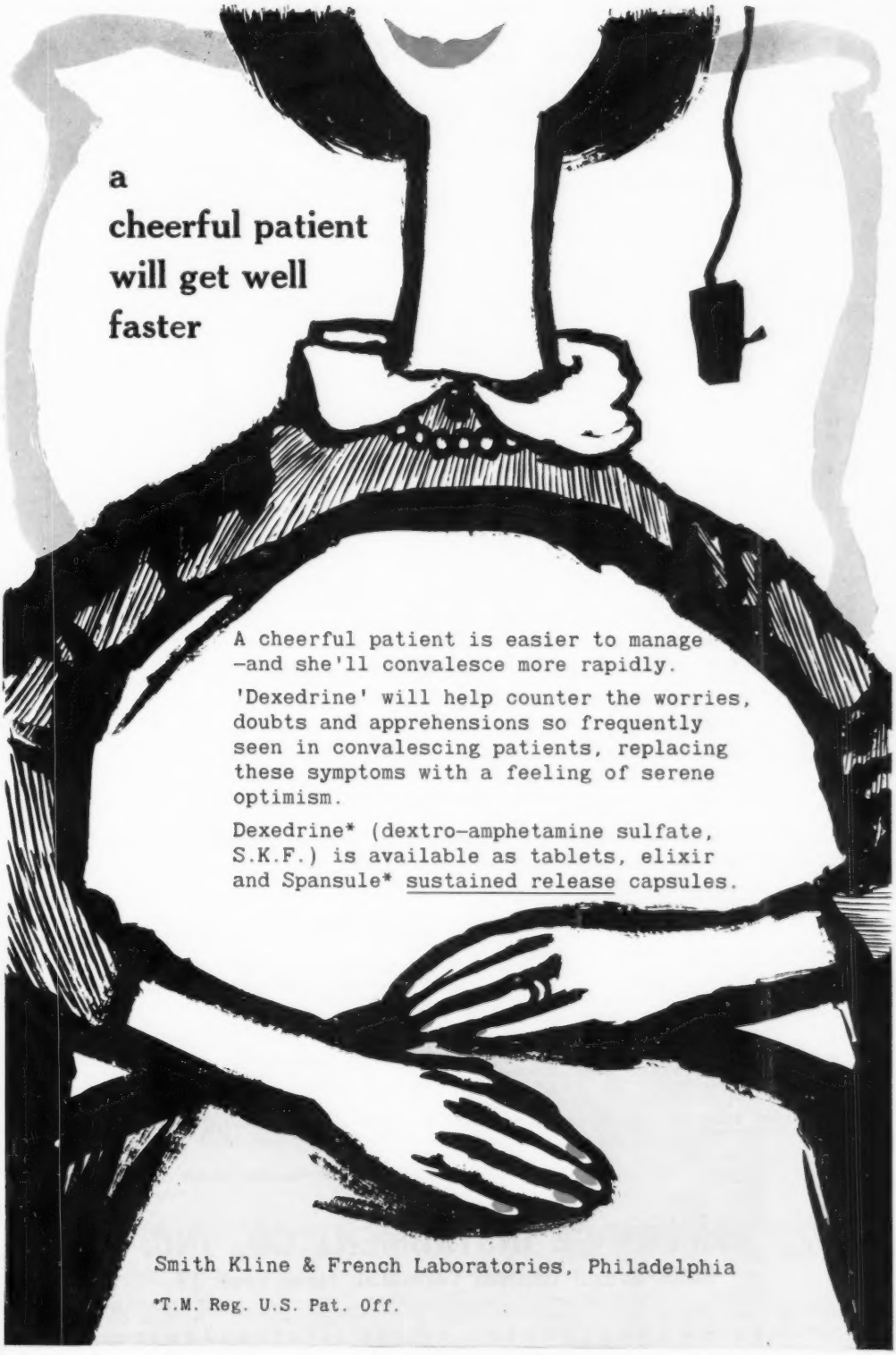
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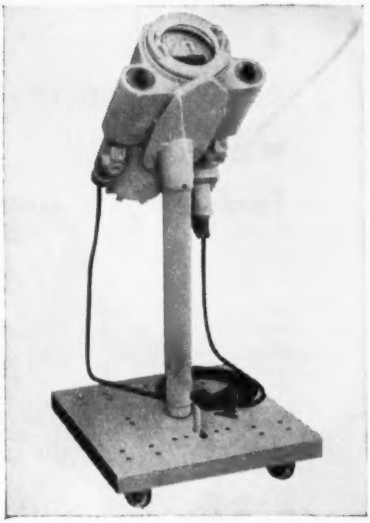

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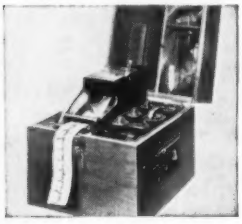

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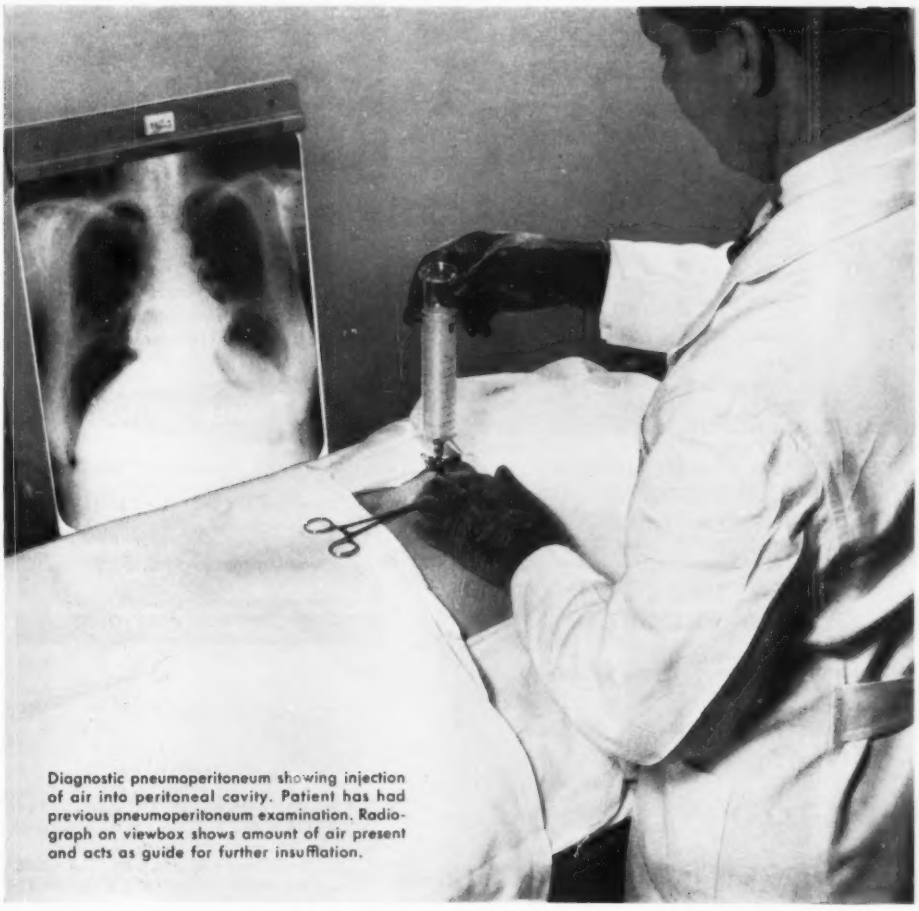

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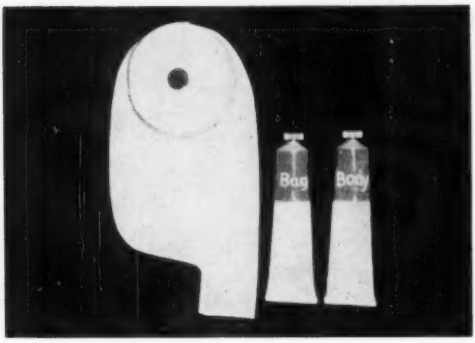

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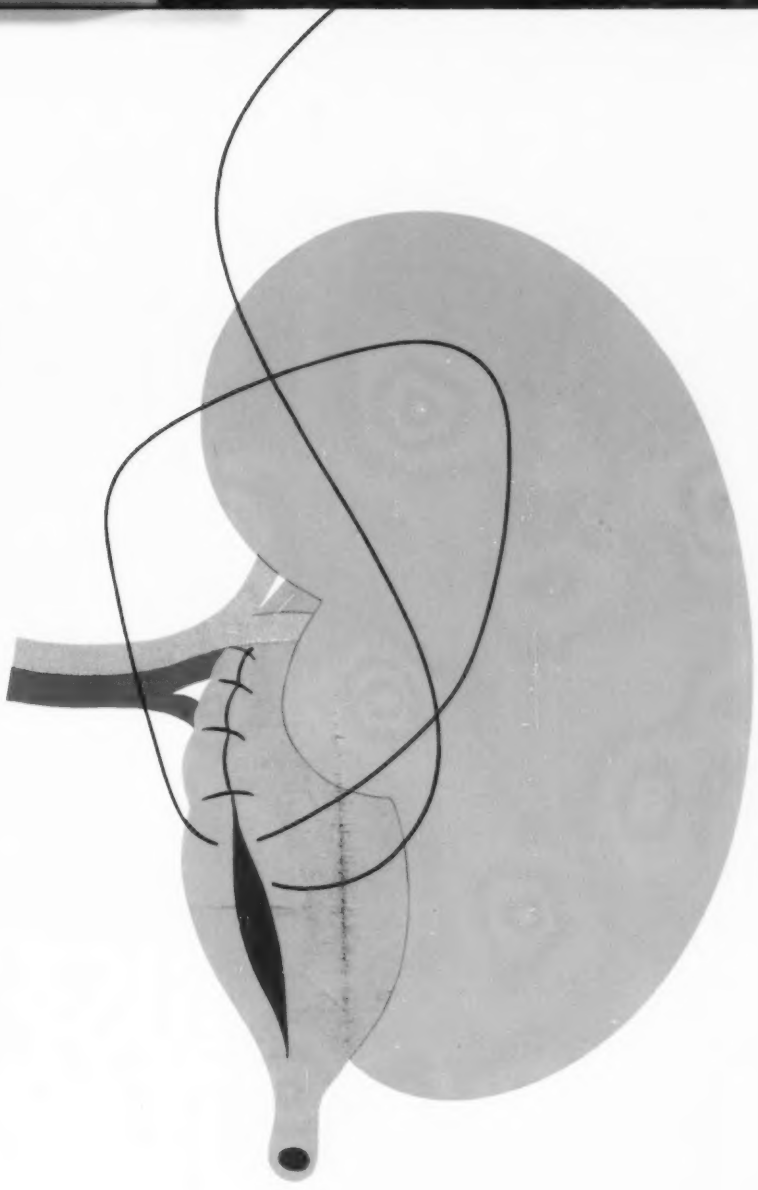

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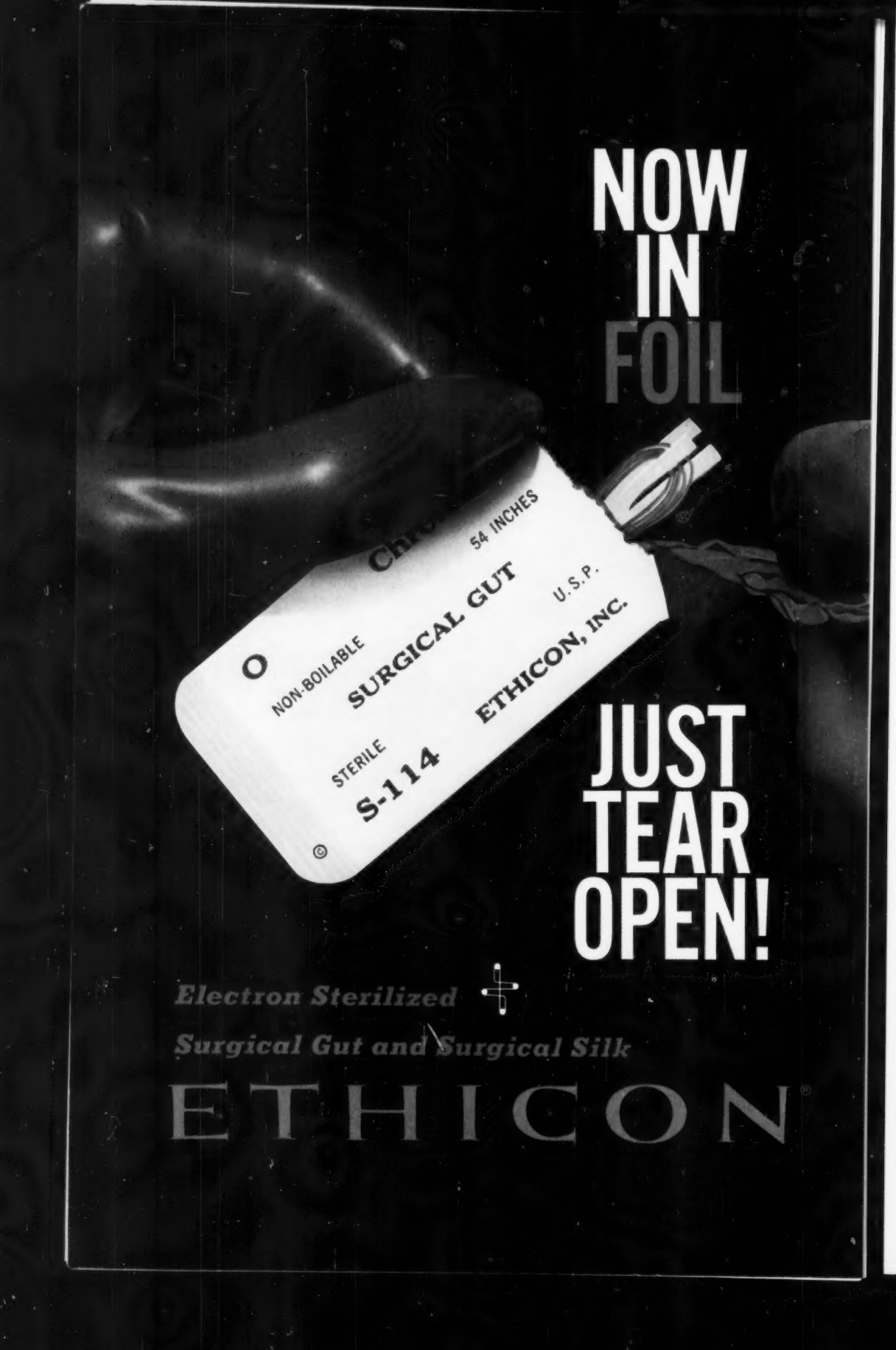
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0.15% solution, vials of 100 cc.

"Niphanoid," ampuls of 250 mg.

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Pontocaine (brand of tetracaine) and Niphanoid, trademarks reg. U.S. Pat. Off.